TUBERCULOSIS AT THE CROSSROADS*

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Tuberculosis was described by Bunyan as "Captain of the men of Death." Perhaps the most important fact about tuberculosis is that it no longer holds that pre-eminent title. But it is still the main killer of youth in its prime, and causes in this country nearly one-third of the deaths between the ages of 15 and 39 and a total of 24,000 per annum at all ages. As a cause of death phthisis has been declining throughout the period since deaths were first registered and classified in 1838—i.e., nine years before the appointment of Dr. Duncan as first medical officer of health in Liverpool (Ransome, 1915). The decline has been remarkably continuous and steady since that date, though fluctuations are noticed at times, epidemics of influenza (e.g., 1890) and the two world wars being occasional causes of temporary rises. Generally when these events had passed the decline continued as before. What, then, has been the major cause of its decline? It is chastening to take the long view in this matter.

Tuberculosis mortality, like infantile mortality, has always been regarded as one of the best indices of the sanitary well-being of a community. The causes of the great reduction of infantile mortality are complex, and it is not easy to give each factor its appropriate weight. May not the causation of the fall of tuberculosis mortality be likewise complex? Certainly to regard this mortality rate as a sensitive sanitary index is a clear indication that we consider the reasons for its fall to be complex.

In 1847 the English mortality from phthisis was 3,189 per million, and the female mortality was higher than the male; nearly a century later the standardized death rate was 528 per million—i.e., one-sixth of what it was in 1847—and the female mortality was 53% of that of the males.

Tuberculosis Mortality in Infancy

The ages at death also show some striking differences. In 1860 18% of the deaths from tuberculosis in Liverpool were at ages under 5 years; and in 1880 the proportion was 32%; in 1946 the proportion was 6.5%, or only about one-fifth of the 1880 figure. It is, however, reasonable to ask whether all the infantile deaths ascribed to tuberculosis in 1880 were in reality so caused. One may question the significance of diagnoses such as *tabes mesenterica*, and be in doubt whether that title did not include deaths from prematurity, marasmus, enteritis, etc. If we consider deaths from tuberculous meningitis we find that equally important changes have been taking place, more especially in infancy and childhood. I have obtained from the Registrar-General, and have taken out from the Liverpool records, the deaths at ages under 1, 1 to 5, 5 to 10, and so on up to 25 years of age, since 1915. One of the difficulties in investigating tuberculosis records is to be sure that one is dealing with comparable statistics, and it is for that reason that the

figures go back to only 1915; before then differences both of nomenclature and of tabulation would gravely complicate comparisons. What is shown, however, is remarkable. In Liverpool the crude mortality during the first year of life in 1947 was only 9% of that recorded in 1915; in the next four years of life it was 18%, from 5 to 10 years 26%, from 10 to 15 years 40%, and at higher ages the reduction is smaller. But the total phthisis mortality has only been halved in these twenty-eight years. Similar, though not so pronounced, reductions in the deaths of infants ascribed to tuberculous meningitis have occurred in England and Wales. The higher the total tuberculosis mortality the greater the proportionate reduction in the meningeal fraction of that total. In the middle of last century many deaths of infants were ascribed to acute hydrocephalus or to cephalitis, the word meningitis seldom being used.

What is the significance of this rapid reduction in tuberculo-meningitic mortality? Tuberculous meningitis ensues when a tuberculoma in the brain or meninx infects the water-bath in which the brain lies; the tuberculoma in this case is the result of a blood-borne infection arising, as a rule, in a primary infection. It would appear, then, that this very rapid reduction in meningeal deaths results from a quite considerable reduction in infection of infants with the human bacillus, or at least of massive infection. That this rapid rate of reduction follows upon the passing of the National Insurance Act, 1911, and the inception of sanatorium benefit and the setting up of tuberculosis departments generally may be no coincidence. In Denmark in 1945 only 28 deaths from tuberculous meningitis took place, of which four were in Copenhagen. This observation may be a valuable clue in the tuberculosis labyrinth. One thing is sure: it bears little or no relation to the improvement of milk supplies or the pasteurization of milk. The case for these as preventive of tuberculous peritonitis and of bone and joint disease needs no further comment; it has been adequately presented by Wilson (1942) and is conclusive. Every case of tuberculous meningitis in childhood should be regarded as a pointer to a dangerous open case of respiratory tuberculosis in the immediate *entourage* of the sick infant; this case should at once be sought and the appropriate action taken when found.

In comparison with a guinea-pig, man is resistant to attack by the tubercle bacillus. He cannot presumably be infected by a single bacillus as can the cavy. Every overt case of tuberculosis is an example of a breakdown of resistance. Repeated massive doses of infection, especially in infancy, provide one of the methods by which that resistance is overcome. Any measures which tend to reduce or prevent such massive infections will be preventive of tuberculosis—the disease that kills and maims. I have used the tuberculo-meningitic mortality as a possible index of a reduction in massive infection; other evidence will appear later. But, regarding the continuous decline in phthisis mortality for over a century, even with the greatest regard

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for the sanitary achievements of Duncan and his successors we cannot think of sanitation as the major factor in the reduction.

Social and Economic Factors in Tuberculosis Causation

We must accordingly seek for a cause for the reduction in some more general factor of social amelioration which would affect the resistance of the mass of the population; for the general occurrence of infection within the first twenty years of life—at least of *urban* life—is widely recognized. This belief is based primarily on the findings of Naegeli (1900) in Zurich and of Burkhardt (1906) in Dresden. Naegeli found evidence of tuberculosis in 17% of necropsy examinations in those under 18 years of age; but in those over 18 years old the proportion was 93%. Burkhardt found the proportions in the same two age groups to be 38% and 91% respectively. When the use of the cutaneous tuberculin reaction was applied by von Pirquet (1911) to children in Vienna in 1909 he found that in the age group 13–14 years no less than 91% of the children reacted positively. These results relate to urban populations. The Prophit Survey (1948), applying the Mantoux reaction to student nurses from Wales and Ireland upon entry into hospital, found 26% negative reactions as against 18% negative amongst English nurses. In England there was only a small difference between the percentages of negative reactors among nurses of urban (18%) and rural (20%) provenance, but in Wales and Ireland the proportions were 19% and 35% respectively. It is evident that in recent years in the rural parts of the British Isles, more especially Wales and Ireland, infection with tuberculosis has by no means been universal, even if we take into consideration that a proportion of the negative reactions may once have been weakly positive and have subsequently reverted. Among London medical students only 14% were *negative*; in students in some universities in the United States the proportion is reversed and only 10–15% were *positive*.

Some economists have used the price of wheat as an index of nutrition, and a close correlation was found in some countries, notably Germany, between this figure and that of the phthisis mortality; but Sir Arthur Newsholme pointed out that in France and Ireland there was no such parallelism. This is not surprising, for money is constantly changing its value in relation to goods.

When for the price of wheat we substitute the “real value of wages”—i.e., what you can get with the money you earn—as was done by Ewart in 1923, there is revealed a remarkably close inverse correlation during the period 1851 to 1915 in England and Wales. Malnutrition and famine have again and again been shown to be productive of a rise in tuberculosis mortality. The 1914–18 war appeared to indicate fat shortage as productive of a rise in deaths from phthisis; the rise was earliest and greatest in blockaded Germany, later and smaller in Great Britain, where U-boat warfare limited imports, and latest and least in the United States, where the shortage was least felt. Shortage of fat-soluble vitamins was present in greater or lesser degree, but Danish and Swedish experiences negative a shortage of vitamin A as the main factors in the increase. There was also a shortage of first-class proteins according to Faber (1938), and he regarded this as the more important. It is not practicable to pin the effects of malnutrition to the deficiency of one ingredient of the diet. The part played by fatigue in the liability to develop clinical tuberculosis in wartime must not be overlooked (M.R.C., 1942).

During the 1939–45 war the rise in deaths from tuberculous meningitis and in young adults in this country pointed to factors other than nutrition being operative, and the

increased exposure to infection in air-raid shelters or elsewhere appears to have been a major cause. This rise reinforces the belief that a high proportional rate of mortality from meningitis indicates a high degree of massive infection in infancy and childhood.

The real value of wages gives a measure of the capacity of the average citizen to acquire goods, but it does not indicate how this capacity is distributed among the population or on what goods it is expended. The Registrar-General's figures show the heaviest incidence of tuberculosis to be upon the lowest-paid workers—i.e., social Class V—whose tuberculosis mortality is double that of the professional Class I.

Numerous coefficients have been calculated (see especially Hart and Wright, 1939) which show a significant high association of tuberculosis mortality on the one hand and poverty, pauperism, substandard housing, and overcrowding on the other. Hart and Wright applied the method of partial correlation,* which endeavours to weight the several possible factors taken into consideration. The significance of overcrowding appeared to be increasing. There can be no doubt that poverty is closely associated with tuberculosis, and that tuberculosis also causes poverty. Poverty is accompanied by malnutrition, bad housing, and overcrowding, the last tending to produce close personal contact with open cases. In view of the great overcrowding in so many of our great cities we cannot expect any automatic reduction in tuberculosis in the near future. As McGonigle observed, better housing without a rise in real wages may, owing to raised rents, lead to deterioration in nutrition.

The steady rise in the real value of wages seems to have been a major cause of the reduction of tuberculosis mortality, but this rise was checked at the turn of the century and reversed during the 1914–18 war (Hart and Wright, chart 4), and appears to have been reversed in and after the 1939–45 war. Thus the index of real earnings, which was 127 in 1875, had risen to 244 in 1939 and has fluctuated since then. A fall in this index also occurred in the 1914–18 war, reaching 176 in 1913 and falling to 146 in 1916; it rose, however, to 205 in 1920. The economic effects of the recent war have, however, been more serious than in the previous war, and we cannot anticipate any such quick recovery. If this rise in the real value of wages has indeed been the cause of the decline of tuberculosis during the nineteenth century it is urgent that we take stock of the position in which we now stand. At the present time there is a world shortage of foodstuffs accompanied by a high world level of prices of transportable foods. To expect an early resumption of the increase in the real value of wages in this country—though possibly not in the United States—would be tantamount to being blind to the most salient economic feature of the times in which we live. If we translate increased real value of wages into terms of better nutrition and housing, involving greater resistance and less exposure to infection in the home, are these really the sole causes of the reduction of mortality in the past?

*Coefficients of correlation (i, v, and vi are from Pearl, 1940):

(i) Tuberculosis mortality in <i>arrondissements</i> of Paris, 1911–17, and the proportion of the population so poor as to be not assessed to house tax	+0.977 ± 0.004
(ii) Total pauperism and phthisis in England and Wales, 1866–1903 (Newsholme)	+0.89
(iii) Mortality for respiratory tuberculosis and substandard conditions of housing in 76 county boroughs (Hart and Wright, 1939), 1931, 1931–3:	
Males 15–24	+0.568
(iv) Ditto: Females 15–24	+0.663
(v) Tuberculosis mortality and overcrowding (more than 3 persons per room) in Vienna, 1897	+0.892 ± 0.047
(vi) Ditto: (more than 2 persons per room) in London, 1908–12	+0.774 ± 0.075

Segregation of Infective Cases

Sir Arthur Newsholme (1908, 1923) gave evidence that there was a close parallelism, especially in later years, between the proportion of deaths from phthisis taking place in hospitals and other residential institutions and the general tuberculosis mortality rate. In 1869-70, when the death rate in England and Wales from respiratory tuberculosis was 24.4 per 10,000 population, only 8.3% of the deaths from all causes occurred in public institutions. "In the year 1920, 36.2% of the total male and 26.5% of the total female deaths from phthisis in England and Wales occurred in hospitals, commonly after prolonged, and often repeated, stay of the patients in these hospitals." Newsholme's figures were severely criticized by Alice Lee (1915) on the ground that his measures of segregation were badly chosen. Power (1908) had earlier cast doubts on the validity of Newsholme's conclusions as applied to the nineteenth century.

I have been able to investigate the matter further, so far as it relates to deaths from tuberculosis (mainly phthisis) in the hospitals and institutions of the city of Liverpool during the period 1860 to 1946, by taking samples at five-yearly intervals, as shown in the following table:

Year	Percentage of Deaths from Tuberculosis in Residential Institutions	Mortality from Tuberculosis per 1,000
1860	13.7	4.4
1865	17.2	5.3
1870	14.1	4.1
1875	17.4	3.8
1880	14.4	3.7
1885	21.7	2.9
1890	20.9	2.7
1895	27.6	2.8
1900	37.2	2.5
1905	44.2	2.0
1910	50.5	2.0
1915	35.8	2.0
1920	42.7	1.7
1925	51.0	1.5
1930	51.1	1.4
1935	60.0	1.1
1940	55.1	0.9
1946	57.2	0.9

From these figures we obtain a coefficient of correlation of -0.94 ± 0.017 , which indicates a very high degree of inverse association. It is subject to the criticism that the array of figures is too small for accuracy, but *a priori* it appears probable that the increasing removal of cases of open tuberculosis to hospital has had considerable influence on the reduction of tuberculosis in this country and elsewhere, especially during the present century. One may well think that this factor has played an increasing part in that reduction since the introduction of sanatorium benefit in 1911. The prohibition of indiscriminate expectation may also have helped in reducing infection.

At this point we must face present realities. At the end of 1946 in this country, despite the addition of 2,440 to the number of "tuberculosis beds" provided, there was a waiting-list of 7,025 tuberculous patients (Ministry of Health, 1946). This position arises from a shortage of nurses, especially of sanatorium nurses, and not of beds. In sanatoria the occurrence of a case of tuberculosis among the nursing staff is, in my experience, exceptionally rare. The mortality from tuberculosis among nurses is no higher than that of the general female population of the same ages, but the morbidity would seem to be higher. Any active campaign against tuberculosis, whether preventive or curative, is at present in this country absolutely dependent upon adequate provision of hospital beds. If we investigate anti-tuberculosis programmes in either Scandinavia or the United States there appear to be waiting *beds* rather than waiting-lists.

The former standard of one sanatorium bed per tuberculosis death per year is certainly out of date. The actual provision in England and Wales is 1.3 beds per death (in Liverpool 1.5), but in Germany it is 2.2 (0.7 in Berlin) and in Canada 2.5; coming to Scandinavia, in Stockholm it is 2.5, in Copenhagen 2.8, and in Oslo 3.0. It is necessary to make the best possible use of available beds, both for the cure of the individual patient and, with emphasis, for the achievement of the best preventive result.

Tuberculosis Among Nurses

I do not think any responsible person in charge of a hospital admitting patients suffering from tuberculosis can be happy about present conditions, under which Mantoux-negative nurses, medical students, and others come into contact with infectious cases. To find that such a person is tuberculin-negative and presents no x-ray evidence of a prior infection seems to require some attempt at least to increase specific resistance, even if complete immunity is out of the question. How far the Bacille Calmette-Guérin (B.C.G.) or the vole bacillus can meet the case I will discuss later. This is a matter of serious importance if we are to continue to nurse infectious, often advanced, cases of tuberculosis away from the home, for it appears highly desirable to increase the proportion of sputum-positive cases so isolated.

One of the factors causing inadequacy of the beds available for the treatment of tuberculosis is the increase in the average length of stay in sanatoria, which now often amounts to twelve months or more. This arises partly from the commendable wish of sanatoria physicians to do the best for their patients and partly from the increasing armamentarium, both medical and surgical, available for treatment. Earlier diagnosis by mass radiography or otherwise has, of course, an opposite effect if the early case can be admitted at once, but often this cannot be done. It is deplorable that such patients have to wait for admission while the most favourable moments for curative treatment are slipping away and while they are possibly becoming sputum-positive, to the danger of their families. In 1938 as many as 65% of patients admitted to sanatoria in England and Wales were classified as intermediate or advanced cases.

Alterations in Ages at Death

There is another aspect of the epidemiology of tuberculosis which should be emphasized—namely, the marked differences between the resistance of races that have for long been exposed to tuberculosis and those that have not. Calmette (1923) presented the evidence fully and I have summarized it (Stallybrass, 1931). There can be no question of the reality of these racial differences in resistance to tuberculosis. Cobbett (1925) expanded Calmette's law of tuberculosis into the following: "Peoples are more resistant to the attack of the infectious diseases of their own countries and districts than to that of foreign diseases with which neither they nor their ancestors have been accustomed to come in contact." Among pygmies brought into this country from Africa the disease is rapidly fatal and epidemic in incidence; among Jews who have lived for centuries in towns, often in ghettos, the resistance is high. This clinical difference in the course of the disease is accompanied by a considerable variation in the age at death. Drolet (1930) has published a diagram contrasting the distribution of male tuberculosis deaths per 1,000 among negroes and Jews respectively age by age in 1926-8 in New York City. Both races lived under closely similar housing conditions. This diagram emphasizes two points: (a) the mortality in the first four years of life was about 60% higher among negroes than among Jews; and (b) the peak age at death is about 25 years among negroes and about 45 years among Jews, a

difference in modal age at death of about 20 years. Such differences of age at death may be regarded as due to the survival of the fittest following Darwinian selection over a long period.

In Liverpool in the past 90 years there has been a marked reduction in the *deaths* attributed to tuberculosis in the first five years of life. Bearing in mind what was previously said in relation to meningitis and tabes mesenterica, the proportion of infant deaths to the total mortality has markedly fallen. In 1860 it was 15.8% and in 1935 0.8%, but it showed a rise in 1942 to 2.6%, mainly attributable to meningitis. Similar but smaller fluctuations occurred in all ages up to 5 years.

Again in Liverpool, the peak age at death was 20–25 years in 1860–70; that period included the Lancashire cotton famine. It rapidly rose to 30–40 years by 1875, and has so remained with the single exception of 1943—following the air raids—when it fell back to 25–30. There has in fact been a considerable shift towards older ages, even up to 90. In Copenhagen and Stockholm there has been a shift towards younger ages in the *death rates* by ages.

The changes in the Liverpool figures closely simulate Drolet's racial differences. But it is hardly credible that Darwinian selection could have affected these changes in a mere 80 years: social and economic changes seem to provide a more probable explanation.

Differential Sex Mortalities

In 1838, when deaths were first registered, the female tuberculosis death rate was higher than the male. The rates crossed in 1860, and by 1925 the males constituted 60.2% of the total. With the increasing entry of women into industry the *proportion* of female deaths has somewhat increased. In 1901–10 (Newsholme, 1923) there was in urban districts a peak age at 45 for men and at 35 for women, the male rate at those peak ages being 166 per 100,000 in excess of the female rate. In rural areas both sexes had a peak mortality at 25 years and the male excess was slight. The differences in the peak death rates between the sexes had been considerably reduced by 1938–9, being equal to a male excess of 25 per 100,000, but the male peak age had further advanced from 45 to 55 years.

These age and sex differences and changes are closely related to occupational causes. Before the industrial age women worked in the home and were exposed to infection from cases never isolated. Exposure to industrial conditions, especially silica dust, introduced a more chronic form of tuberculosis affecting men; lately the increase in the number of women in industry has increased their exposure to infection, and this was especially true in wartime; at the same time advances in the hygiene of the dangerous trades have tended to reduce the male excess. It would be of interest to know at the next census just what part of the male excess is attributable to the excess tuberculosis mortalities of these dangerous trades. Alcoholism plays a part in the excess male mortalities, but less so than in the past.

Results of Tuberculin-testing

One of the great advances in recent years in our knowledge of the epidemiology of tuberculosis arises from the increasing use of tuberculin for testing that sensitization of individuals which is caused by infection with the tubercle bacillus, whether natural or artificial. The refinements of the Mantoux test with its increasing test dosage of tuberculin have improved the sensitiveness of the method and rendered it superior to the von Pirquet test, which may be negative when the Mantoux test is positive. For this purpose old tuberculin, which contains two proteins of differing

antigenic properties, is commonly used, but in the United States and Denmark P.P.D. (purified protein derivative) is in general use. In either case it is a test of allergic sensitization and not of resistance—much less immunity—but the parallelism between allergy and resistance appears to be sufficient to permit the measurement of the allergy as a rough test of the degree of resistance. It is unfortunate that owing to variations in the strength of the tuberculin used for testing—noticeably in Norway—the results of tuberculin-testing in one country are often not strictly comparable with those in another.

From the extended use of the Mantoux test it is now known that effective infection with *Mycobacterium* is not so widespread, especially in rural populations, as appeared to be the case early in the twentieth century, *pace* Naegeli, Burkhardt, and von Pirquet; later studies of Schuermann (1929) showed pulmonary lesions in only 1.7% of necropsies of those under 30 years of age and 11% of those between the ages of 30 and 45. Many negative tuberculin reactions are found among primitive communities (Topley, 1933), a high proportion of positives among most civilized communities, and a lower percentage of positives in the United States and Scandinavia, especially among those who, from rural location or economic shelter, have probably escaped contact with the bacillus. In Stockholm, states Heaf (1947), at 7–8 years only 8% were reactors and at 13–14 years only 26%. In Stavanger only 22.4% were positive at 10–20 years. In Denmark nation-wide figures show that two-thirds of the population are negative at 14 years; at 20–23 years the proportion is one-third (Holm, 1946). But in Scandinavia, where the use of B.C.G. is rapidly extending, the aim is to raise the proportion of positive reactors artificially. It is considered almost antisocial not to be tuberculin-positive.

The results of x-ray examinations largely confirm the results of the tuberculin tests. Holm states that a great part of those undergoing natural conversion show very prompt x-ray changes. Nevertheless the results of the Prophit Survey (1948) revealed that radiologically visible changes were seldom found when a recent primary lesion had caused a Mantoux-conversion from negative to positive—namely, 7.6% among nurses and 8.5% for London medical students. Malmros and Hedvall (1938) reported 13.9% of the naturally Mantoux-converted showing primary lesions. The Prophit Survey further states that the morbidity following primary infection was proportional to the degree of tuberculin sensitivity noted on natural Mantoux-conversion.

It should be the ultimate objective in tuberculosis control finally to eliminate these *natural* Mantoux-conversions. The Prophit Survey considers that “at the present stage of tuberculosis epidemiology it would be vain to hope to suppress all sources of infection and protect every person from even small infections. Nevertheless, no rational theory of prevention can be based on the theory that stray small infections produce a beneficial immunity. An entirely uncontrolled immunizing process responsible for many thousands of deaths can have no scientific support. Public health measures should therefore be directed to reducing exposure to a minimum. . . . Certainly even if occasional infection cannot at present be prevented much heavy repeated exposure is largely avoidable. The Prophit results have confirmed the importance of repeated exposure as one of the factors in the development of tuberculosis.”

Obviously such a view excludes any belief that exposure to natural infection by bovine bacilli can serve any valuable purpose. The figures (Prophit Survey, 1948) relating to the marked decline in tuberculosis mortality in the United States at a time when bovine tuberculosis in cattle has been almost eliminated and pasteurization has become general show that the virtual elimination of infection by

bovine bacilli in man has not served to retard the concomitant fall in respiratory tuberculosis mortality.

But such a view will not be applicable to the use of avirulent tubercle bacilli for artificially increasing resistance to tuberculosis, of which the Bacille Calmette-Guérin is the only strain that has undergone prolonged test; still less would it apply to the vole bacillus, now under trial. Indeed, the Prophit Survey Report says: "Serious consideration should be given to the possibility of undertaking *in this country* [my italics] investigations into the vaccination of tuberculin-negative young adults, such as hospital workers, entering conditions of particular exposure." The same action is equally indicated in relation to any tuberculin-negative contacts of open cases of tuberculosis.

The Prophit Survey has also thrown light upon the vexed question whether tuberculosis in young adults represents infection, reactivation, or reinfection. The application of Mantoux-testing and radiography enables the first to be largely eliminated so far as the tuberculin-negative are concerned. Formerly much importance was attached to reactivation of old foci, but the proportion of cases of reactivation is possibly smaller than formerly believed. Reliable observations show it to be probable that reactivation of a calcified focus seldom occurs, as the bacilli contained therein are dead, though Blacklock (1947) was able to isolate bovine bacilli from calcified glands. This outlook stresses the importance of the prevention of massive and/or repeated infection.

Control of Contacts

In the prevention of infectious disease the *control* and immunization of contacts often play the most important part. The greatest attention has been given to the examination and *observation* of contacts of tuberculosis, but of control in the epidemiological sense there has been little in this country. In France and elsewhere the "œuvre de Grancher" consists in the removal of the infants of tuberculous parents—especially mothers—for an indefinite period. This can be regarded as a counsel of despair: the removal of the patient would appear to be the better plan if no other solution were possible. In Scandinavia the newborn infants of tuberculous parents are vaccinated at birth with B.C.G. and segregated for ten weeks or thereabouts because of the comparatively slow development of immunity in the infant; they are then returned to their homes. Heaf (1947) states that no vaccinated infant in any of the Scandinavian countries has so far succumbed to tuberculous meningitis or miliary tuberculosis. Contrast with this the figures relating to Black Notley Sanatorium, where the tuberculous mother is confined under the most favourable circumstances and is instructed in the prevention of infection of her child. Despite these precautions, of 11 children who were in contact with sputum-positive mothers four contracted tuberculosis and two died—i.e., 36% morbidity and 18% mortality.

There can be no question whatever about the importance of familial contact with tuberculosis. Deeny (1947) showed that in a town in Northern Ireland one-third of all the deaths from tuberculosis occurred in houses where there had been two or more such deaths. Opie and McPhedran's (1926) figures contrasting the rapid development of Mantoux-positive reactions in the child contacts of tuberculous patients in comparison with non-contacts fully demonstrate the importance of infection in the home. Stewart *et al.* (1937) obtained figures of the actual morbidity of contacts in rural areas of Tennessee. They showed that the incidence of subsequent cases in a tuberculous household was 2.06% in the year of onset, 1.33 in the first year following contact with the index case, 1.15 in the second, and lesser figures in the succeeding years.

We may conclude that in the causation of tuberculosis there is an uneasy balance between an increasing resistance—not to infection, but to morbidity and mortality, such resistance being partly racial or genetic, partly nutritional, the latter being closely related to the increase in the real value of wages during the nineteenth century—and massive and/or repeated infection, especially at susceptible ages, as in infancy, and later in adolescence and young adult life. Such massive infection has been greatly reduced throughout the past 80 years, and, speaking generally, increasingly so during the present century. The reduction of exposure in infancy results in an accumulation of susceptible tuberculin-negative adolescents and may cause a relative increase in tuberculosis in young adults because the risks of repeated exposure are much greater in the tuberculin-negative. This susceptibility can be overcome to a considerable extent by the production of artificial resistance. Sili-cosis, and possibly other adverse industrial conditions, may account for greater and later male mortalities compared with those of females.

Vaccination Against Tuberculosis

B.C.G. is a living avirulent strain of the bovine bacillus which, after 230 successive cultures over a period of 13 years, was employed in 1922 for the vaccination of children born in tuberculous families. It gives a "normal" tuberculin, but has never been recorded as having returned to virulence or produced a general infection in any of the more than 3,000,000 children said to have been vaccinated with it in the past 26 years. Nevertheless the Pasteur Institute has not yet accorded it the status of "virus fixe." All the cultures now used for inoculation are derived from this strain. The Lübeck tragedy was caused by the admixture of virulent bacilli with the B.C.G., and those responsible were convicted of gross carelessness. It is for this reason that B.C.G. should be produced in a laboratory entirely dissociated from other bacteriological work.

Recently by the kindness of Drs. Bøe and Krohn I was enabled to see the Nasjonalforeningen B.C.G. Laboratorium in Bergen, where all the B.C.G. used in Norway is freshly prepared every week; the vaccine should be used within ten days of production, as it is apt to weaken owing to the death of the bacilli. It should therefore be kept in a refrigerator or ice-box. Two strengths are produced, clearly distinguishable by sight, one being obviously turbid and forty times as strong as the other. The stronger one is used only for transcutaneous inoculations. The more dilute emulsion is clear, and is employed for intradermal inoculation. Myren (1948) states that on a certain occasion the stronger emulsion was accidentally used for intradermal inoculation of 66 persons; localized ulceration was the only untoward effect, and the immunity produced appeared to be more durable than ordinarily. However used, it is important, as Holm (1946) points out, that the virulence of the B.C.G. strain should be kept at a proper level, and the bacteriologist at the B.C.G. Laboratory should be kept informed of the results of every inoculation.

The intradermal method has been more generally used, 0.1 ml. of vaccine being injected. It has the advantage that the dosage is more certain; it has the disadvantage that if through poor technique the injection is given subcutaneously a small localized abscess with enlargement of neighbouring lymph glands will ensue. Bacilli from such an abscess are, however, avirulent when cultured. Even so injected the discomfort is minimal and not incommensurate.

The transcutaneous or multipuncture method does not suffer from this disadvantage. Birkhaug (1944) gives theoretical grounds for the belief that the skin itself is an antibody-producing organ. Birkhaug's original instrument

released forty needle-points automatically; its use has been given up in Bergen, and five or fewer applications of a holder fitted with eight gramophone needles are substituted. The skin is first cleaned with ether, the thick emulsion vaccine is then spread from a syringe with a needle, and the multipunctures are made. Statistical material is still being collected to evaluate this process. In Bergen, of 10,568 inoculated some 7,894 were controlled after two months; of these, 7,472 (94%) were Mantoux-positive. This result is in no way inferior to those of the intradermal method (personal communication). The objection that Birkhaug's instrument was difficult to sterilize has thus been overcome.

It is a strict rule that all persons must be Mantoux-tested before inoculation, and only those who do not react to 100 tuberculin units (Holm, 1946) should be inoculated. In a few cases men have been inoculated by accident during the allergic state without any untoward result—i.e., there is no negative phase, though an accelerated reaction may occur (Koch's phenomenon). The normal response is that at the end of three weeks raised papules appear at each puncture point. In six weeks a positive Mantoux reaction is usually obtained. In infants this may take ten weeks or even more. For infants 16 punctures, for women and children 24 punctures, and for men 40 punctures are given (Birkhaug, 1944). The use of B.C.G. involves not only the application of the vaccine in the appropriate way but also, if statistical fallacies are to be avoided, subsequent protection from virulent infection until sensitivity is demonstrated.

Results of Vaccination

So much for the methods; what are the results? Space does not permit a full description of even the better-documented experiences relative to but a small fraction of the 7,000,000 persons who have, according to Myers (1948), been vaccinated with B.C.G.; the majority of these have received the vaccine orally. The matter has been discussed by Holm (1946), Aronson and Palmer (1946), Wilson (1947), Heaf (1947), Levine (1947), Malmros (1948), Wallgren (1948a, 1948b), Rosenthal *et al.* (1948), and Aronson (1948). An Empire Conference in London, international conferences in Washington and Paris, and annual conferences in Scandinavia have taken place. The examples below—mainly from Scandinavia, where B.C.G. inoculation is practised on a national scale—are recorded for their apparent success. Given singly, they might not carry conviction to the critical mind; taken collectively, even the hypercritical cannot fail to reach the conclusion that in the varied circumstances the use of B.C.G. has been not merely harmless but endowed with marked protective properties.

1. In the Swedish district of Orebro (Malmros, 1948), in a population of 230,000 there have since 1942 been 22,413 vaccinated with B.C.G.—i.e., 8,040 newborn, 7,836 children over 1 year, and 6,537 adults. During the period 1942–7 only one vaccinated person has been regarded as tuberculous: a nurse, twice vaccinated, developed pleural effusion; there was no definite evidence of tuberculosis. This example does not provide a contemporary control.

2. The island of Bornholm, in Denmark. The comparison here is before and after a period of intensive testing and inoculation since 1945, by which time 10,337 young persons—i.e., 23.3% of the population—were vaccinated (Olsen, 1947; Malmros, 1948). A marked fall in the incidence of tuberculosis resulted at just the ages—namely, 7–35—at which vaccination took place. Notifications fell from 134 in 1935–40 to 82 in 1941–6. The proportion vaccinated is now 27%; 98% of those found tuberculin-negative and offered B.C.G. accepted.

3. Hyge's report on an outbreak in the Aurehoej State School in Denmark (Holm, 1946) has the force of a laboratory experiment, but was excluded by Wilson from his survey of the subject. The school had had Mantoux-testing followed by

voluntary B.C.G. vaccination, the last tuberculin-testing being in December, 1942. The 368 girls were then in three classes: (a) naturally Mantoux-positive, (b) Mantoux-negative who had had B.C.G., and (c) Mantoux-negative who had not received it. Then in January and February, 1943, an influenza-like outbreak occurred, mainly affecting the unvaccinated Mantoux-negative. Suspicion of tuberculosis was aroused by the occurrence of a case of erythema nodosum. It was found that the source of infection was a teacher who had taught in an ill-ventilated classroom while suffering from a supposed "cold," though gastric lavage later revealed tubercle bacilli. Taking the 305 scholars in her class or classroom, the following results were found:

(A) 105 naturally positive. Four cases of genuine pulmonary tuberculosis. Morbidity, 3.8% $\pm$ 1.95.

(B) 106 negative reactors given B.C.G. Two cases of genuine pulmonary tuberculosis. Morbidity, 1.9% $\pm$ 2.6.

(C) 94 negative reactors. December, 1942. Seventy rapidly inverted to positive reactors. Of these 70 inverters 41 showed x-ray changes and 37 had tubercle bacilli; 55 had initial symptoms, 10 had pleurisy (3–11 months after infection), and 1 had peritonitis. Taking those with symptoms and x-ray changes, the morbidity was 43.6% $\pm$ 10.6.

Among the 63 girls not using this classroom there was no illness, and none of the 11 Mantoux-negative reactors in this group became ill. These figures also bear out the belief, held in Scandinavia, that persons who have undergone Mantoux conversion after B.C.G. vaccination, if they do develop signs of tuberculosis, usually have a short illness of two or three months and can then leave hospital and have no relapse. Comparisons between A or B on the one hand and C on the other are statistically significant.

4. Heimbeck's figures (per 1,000 observation years) relative to the incidence and mortality of nurses at Oslo (Wallgren, 1948b):

	Morbidity	Mortality
B.C.G.-vaccinated	24.1	2.1
Non-vaccinated	141.2	14.6

5. Rosenthal's experience (Rosenthal *et al.*, 1948) with newborn children born in Chicago during ten years. The mothers were interviewed in the hospital and the children vaccinated before they left the hospital. Contrary to what is done in Scandinavia, no isolation of the child before or after vaccination was carried out.

	Non-Contact		Contact	
	Vaccinated	Control	Vaccinated	Control
Person-years and proved ..	5,627	6,032	517	284
Tuberculosis rate	1.95	6.46	3.86	17.60
Hospitalized	0.17	2.48	1.98	17.60
Deaths	1	7	0	4
Death rate	0.17	1.16	0	14.0
Deaths from other causes ..	27	22	3	2

Wilson (1947), after a lengthy review of the present position in regard to B.C.G., concluded that, whilst a presumptive case for the value of B.C.G. has been established, the documentary evidence is insufficient to estimate the degree of protection it affords, and he makes certain other criticisms which, in the opinion of Malmros and Wallgren, disregard much of the Scandinavian evidence quoted above.

In September, 1946, a conference on B.C.G. vaccination was held in the offices of the Tuberculosis Control Division of the United States Public Health Service in Washington, D.C. The deliberations of the distinguished leaders in tuberculosis from the United States and elsewhere concluded from the studies presented to the conference that B.C.G. vaccination confers increased resistance to tuberculosis for the limited period covered in those studies, and that medical literature reveals no proved cases of progressive disease as a result of B.C.G. vaccination, which can

be done without causing severe local reaction. In these studies B.C.G. converted a large percentage of non-reactors into reactors. The need for revaccination and the time interval between vaccination required further study. It was recommended that a single laboratory be established to produce vaccine for the whole country for use in research programmes prepared by the conference, but that it should not be produced commercially.

In America, with an economic outlook that is favourable in comparison with that of Europe and a falling tuberculosis mortality, an expectant outlook to B.C.G. may be permissible. In Scandinavia the question of the value of B.C.G. is now regarded as a *chose jugée*; it has definitely been adopted there on a national scale. In Norway B.C.G. vaccination is compulsory for certain grades of the population—e.g., the eighth-grade scholars. At the meeting of the Northern Tuberculosis Physicians in Oslo in July last the prevailing opinion was that all children ought to be vaccinated from infancy and that it should be repeated in childhood. It is difficult to become a nurse in Scandinavia without being Mantoux-positive or becoming so.

In this country the position is such that we cannot afford not to have available every resource in the combat against tuberculosis; we cannot possibly be complacent in our attitude towards its prevention. The control of contacts is gravely hampered: I have in mind a family of four children, successively infected from a tuberculous mother and all admitted to hospital, whose illnesses, according to Scandinavian experience, could have been prevented. With the shortage of nurses and of hospital beds at least those Mantoux-negative nurses who wish it should receive the degree of protection that B.C.G. affords. As a minimum programme B.C.G. should be prepared at a separate central laboratory, say in London, as is done in each of the three Scandinavian countries. It does not seem to be necessary to wait another five or ten years, by which time experiments may answer some of the remaining questions concerning B.C.G. vaccination, before it becomes available for more general use under conditions of control such as exist in Scandinavia.

Wells (1947) has vaccinated 121 persons with the vole bacillus, and has not observed anything but localized disease or any enlargement of lymph glands. He states that sensitivity to tuberculin following vaccination with the vole organism is greater and occurs earlier than that following B.C.G. Animal inoculation by itself will secure a fixed level of virulence. Tytler stated that its safety "appears unquestionable, but can hardly be greater than that which practice has proved for B.C.G." (See also Wells, 1946.)

If adequate control of contacts is to be carried out in this country the staff engaged in the purely preventive side of tuberculosis control must be augmented. If from largely being observers they are to be engaged in actively producing immunity their numbers should be at least doubled. In Scandinavia the proportion of tuberculosis officers, measured either by population or by number of cases, is everywhere considerably higher than in Great Britain. When the people are ready to accept vaccination we should be ready to give it. We need a "new look" in tuberculosis control.

Summary

The great decline in tuberculosis mortality that occurred in the later two-thirds of the nineteenth century was caused mainly by improvement in socio-economic factors of which the rise in the real value of wages is the best gauge. This rise in value resulted from the increasing productivity of machines; it facilitated better nutrition and housing, and in the home it involved a lessened exposure of women, and more especially children, to infective cases. For a period bad conditions in industry weighted the conditions against men, silicosis

causing a high mortality in later male life; the male deaths now considerably exceed the female.

In 1911 a factor previously unimportant followed sanatorium benefit, which provided accommodation for the segregation of earlier cases and became increasingly effective. Previously the deaths in Poor Law hospitals took place there largely as a result of destitution. Despite the pause in the rise in the real value of wages—becoming an actual decline in each of the two wars—the tuberculosis death rate continued to fall—markedly so in tuberculous meningitis in infancy and childhood. It is assumed that this was mainly due to the segregation of infective cases, though improved treatment was not without result. Largely owing to the shortage of nurses, this factor was inadequate during and after the last war and can no longer be relied on. In Scotland tuberculosis mortality is increasing, largely among young adults.

Family contacts of known cases form at least one-third of cases of tuberculosis, and the infection of nurses is a serious defect in our present system. Vaccination with B.C.G. (or the vole bacillus) appears to meet present pressing needs, especially as a preventive for the two classes just mentioned. Twenty-five years' experience of B.C.G. has shown it to be harmless; it is universally adopted in Scandinavia, where its use—compulsory in Norway—has led to a marked decline in incidence and mortality among those receiving it. It is recommended by the World Health Organization that it should be provided free; it should be produced centrally and be used, in the first instance, for the prevention of tuberculosis among known contacts of cases.

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