BIOLOGICAL AND SOCIAL ASPECTS OF TUBERCULOSIS*

The Hermann M. Biggs Lecture

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A LECTURE dedicated to the memory of Hermann Biggs, and devoted to the subject of tuberculosis, calls forth some startling historical facts. Biggs had early become interested in problems of public health and in his bachelor's dissertation when he graduated from Cornell in 1882, he had expressed the view that filth and poor hygiene were the primary causes of contagious diseases and micro-organisms only by-products of disease. This was the official doctrine taught at Bellevue, where Biggs was a medical student, and he had learned it there from Flint's standard text book, "The Principles and Practice of Medicine." The fifth edition of this book, published in 1881 with the collaboration of W. H. Welch, dealt at great length with the subject of tuberculosis and mentioned as its causes: hereditary disposition, unfavorable climate, sedentary indoor life, defective ventilation, deficiency of light and "depressing emotions." The authors added that "the doctrine of the contagiousness of the disease has . . . its advocates, but general belief is in its non-communicability."

It was in 1882, one year after this statement by Flint and Welch, that Koch announced to a startled world the discovery of the tubercle bacillus. Koch's achievement soon brought about a profound revolution in the medical point of view toward tuberculosis, and shifted emphasis from heredity, climate and emotions to methods for preventing the spread of bacilli through the community. The bacteriological era had begun.

Biggs realized immediately all that the germ theory meant for the control of tuberculosis, and his practical and vigorous approach to the problem soon made of him one of the greatest statesmen of public health.

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In the capacity of pathologist to the New York City Health Department, he signed in 1889 with his colleagues Prudden and Loomis a memorable report on tuberculosis. The conclusions were as follows:

1. That tuberculosis is a distinctly preventable disease.

2. That it is not directly inherited; and

3. That it is acquired by the direct transmission of the tubercle bacillus from the sick to the healthy, usually by means of the dried and pulverized sputum floating as dust in the air.

The measures, then, which are suggested for the prevention of the spread of tuberculosis are:

1. The security of the public against tubercular meat and milk, attained by a system of rigid official inspection of cattle.

2. The dissemination among the people of the knowledge that every tubercular person may be an actual source of danger to his associates, if the discharges from the lungs are not immediately destroyed or rendered harmless; and

3. The careful disinfection of rooms and hospital wards that are occupied or have been occupied by phthisical patients.

While the tremendous impact of the germ theory had led Biggs to concern himself chiefly with the spread of infection, he had not forgotten that the bacillus is only one of the factors in the causation of tuberculosis; he emphasized this fact in a popular article entitled "To Rob Consumption of its Terrors," published in the February 1894 issue of the "Forum."

"While tuberculosis is communicable, yet it is communicated with far less facility than many other diseases, which are more properly called contagious. Ordinarily, for its transmission, long exposure to infection, and intimate association with the infected individual, are required unless, because of some peculiar conditions, the natural resistance has been much reduced. Influences which depress the general vitality, or which produce more or less chronic affections of the air passages, increase the susceptibility. Foul air, unhealthy occupations, food poor in quality or insufficient in quantity, impaired nutrition, defective ventilation, certain climatic conditions, heredity, bronchial and pulmonary inflammations, and especially fatigue from nursing consumptives, all act as important factors in creating a soil which is favorable for the development of the tubercle bacillus when once it has gained entrance."

There was nothing original in Biggs' views concerning tuberculosis.

His contribution to the control of the disease was to formulate and implement a practical program based on three simple concepts: 1) to check the spread of infection by identifying the carriers of bacilli and by taking measures aimed at minimizing contacts between infected and non-infected persons; 2) to help human beings in developing a higher resistance by advocating healthy living habits not only for patients in sanatoria, but also for well persons in normal life; 3) to undertake a program of education aimed at mobilizing the intelligent and active coöperation of the community as a whole in the anti-tuberculosis measures. The last point appears commonplace today, but it was then a revolutionary departure in medical and social philosophy. It shifted the emphasis from treatment of the individual patient to the control of disease in society, and it involved a new type of relationship between the medical profession and the public. The whole community was expected to take a constructive part in the fight against disease instead of passively following the instructions of physicians.

Vigorous campaigns based on these three principles were undertaken over much of the Western World during the first years of the 20th century. Particularly in the United States, Biggs had the satisfaction of seeing his policies endorsed by private organizations of physicians and laymen operating under the leadership of the National Tuberculosis Association and by official agencies of public health. When he died in 1923, his goal of incorporating scientific knowledge into a doctrine of action understood and supported by the general public had been reached and he could point with pride to a startling decline in the mortality caused by tuberculosis.

The anti-tuberculosis program has continued to expand throughout the 20th century and the tuberculosis mortality has continued to decrease, in many places at a dramatic rate. Even though mortality statistics are inaccurate and often of questionable significance, it seems worth while documenting this phenomenonal decline with a few figures. Between 1800 and 1850 the tuberculosis mortality reached an annual level of 300-400 per 100,000 population over much of Western Europe and Eastern United States, and was still greater than 200 at the end of the century. In 1925 the tuberculosis mortality in the United States had come down to seventy-five a reduction of 63 per cent in twenty-five years. In 1950 it reached the all time low of approximately twenty-six for the Continental United States as a whole and was less than ten in

some of the Midwestern and Western States. A decrease of the same order has also taken place in several other countries, and one may hope that tuberculosis, which was "The Captain of All the Men of Death" in 1900, is now on the way towards being conquered in the Western World.

The downward course of tuberculosis mortality rate during the fifty years that have elapsed since the beginning of the concerted medical and social efforts to eradicate the disease is an unquestionable fact, but there are skeptics who question whether the anti-tuberculosis campaigns really had much to do with the phenomenon. They point to the fact that tuberculosis mortality had begun to decrease even before the anti-tuberculosis campaign was thought of, indeed before the discovery of the tubercle bacillus. And indeed extensive statistical data indicate that the downward trend began in England and in the United States shortly after 1850. Hospital records suggest a similar situation in other European countries as well.* Neither the discovery of the tubercle bacillus nor the growth of the sanatorium movement, nor the organization of the anti-tuberculosis associations, nor the introduction of pneumothorax therapy, seem to have affected markedly the shape of the mortality curve. As to thoracic surgery, vaccination with BCG, antimicrobial treatment with streptomycin and PAS, they are of such recent origin, or have been used on such limited scale, that they could not have played any part in the phenomenon under discussion.

The skeptics also call attention to another intriguing fact. It is not only the mortality of tuberculosis that has decreased during the past decades, but also that of many other infectious diseases for which there has not been any organized campaign of control. Thus the death rate of pneumonia was decreasing at the same rate as that of tuberculosis even before the introduction of therapy with serum, sulfonamides and penicillin. Several other bacterial diseases such as scarlet fever and whooping-cough have also become less frequently fatal in Europe and North America and have now all but vanished as causes of death in many localities (Table I). Clearly, say the skeptics, we are dealing with a profound biological phenomenon which transcends tuberculosis. Independently of conscious human efforts, something has happened which has increased the resistance of man in the Western World to many

* Curves of mortality rates illustrating these statements are presented in the following article, The Tubercle Bacillus and Tuberculosis by R. J. Dubos, American Scientist, July 1949, pages 354 and 355.

TABLE I — ANNUAL MORTALITY RATES PER 100,000 POPULATION OF PULMONARY TUBERCULOSIS, SCARLET FEVER, WHOOPING COUGH, DIARRHEA AND ENTERITIS IN THE CITY OF NEW YORK FROM 1900 TO 1950*

Year	*Pulmonary Tuberculosis*	*Pneumonia*	*Scarlet Fever*	*Whooping Cough*	*Diarrhea and Enteritis*
1900	.....	.....	13.5	17.0	142.7
1905	212.0	243.0	11.8	10.1	118.4
1910	181.7	219.8	19.9	6.1	115.4
1915	168.9	209.0	5.6	7.6	67.5
1920	108.5	177.0	3.9	10.8	53.7
1925	75.5	132.8	1.2	4.9	38.6
1930	64.2	116.0	0.8	1.8	26.0
1935	55.1	88.6	1.1	2.1	14.1
1940	44.5	45.7	0.2	0.7	10.3
1945	41.5	39.5	0.1	0.5	8.7
1950	29.2	32.3	.....	.....	.....

* Data kindly supplied by Dr. A. E. Cohn and Miss Claire Lingg.

ancient and destructive plagues. It will be shown later in this report that policies of public health have played a far more important role in the control of communicable diseases than the preceding paragraphs might lead one to suppose. For the convenience of the discussion, however, it seems useful to consider first some of the hypotheses that have been formulated to explain the spontaneous decline in tuberculosis mortality during the past 100 years.

In order to account for the progressive decrease in prevalence and severity of tuberculosis, one might assume that tubercle bacilli have become less pathogenic for man, or that man has become more resistant to the bacilli. The first hypothesis is unlikely for tests in experimental animals have so far failed to give any evidence of a decrease in pathogenicity of the bacilli in the course of the bacteriological era. Moreover, tuberculosis today, as in the past, manifests itself with extreme epidemic violence and destructiveness when it attacks populations newly exposed to it, or any group of people compelled to live under conditions of physiological misery. It appears certain, therefore, that the same breed of tubercle

bacilli that caused the great White Plague of the 19th century is still at large in the world today.

But if the bacillus has not changed, its human host certainly has. There is no doubt that the response of man to the damage caused by infection is profoundly affected by many different factors and that some of these have varied in the Western World during the last century. It is probably true that all human beings can fall victim of tuberculosis if they are exposed to heavy infection at a time when their resistance is very low. It is also true, on the other hand, that inbred characteristics can spell the difference between abortive infection and severe disease, between life and death, under ordinary conditions of exposure to the bacilli. While hereditary resistance allows a certain percentage of individuals to go unscathed through widespread epidemics of tuberculosis, the most susceptible often die young leaving no progeny. Thus, familial susceptibility will express itself in smaller number of descendants during periods of epidemics, and it seems to be a fact that many tuberculous families became almost extinguished within a few generations during the 19th century. Only the individuals endowed with some degree of inborn resistance to tuberculosis are likely to survive when the infection rate is high.

The theory of familial susceptibility has received support from the experimental breeding of selected families of rabbits and guinea pigs differing in their susceptibility to tuberculosis. Although it was not possible to obtain animals endowed with absolute resistance, the differences observed between the selected families were sufficiently great to have been of significance under natural conditions of exposure to infection. It seems fair to assume therefore that in man as well, some increase in inborn resistance may have taken place through the selective process brought about by the prevalence of tuberculosis during the 19th century.

Selective breeding of the least susceptive human families is not the only means by which a widespread epidemic can increase the resistance of the population. For it is known that a slight tuberculous infection producing an abortive disease, or one with a slow course, can confer a certain level of immunity which is sufficient to protect against infective doses capable of determining severe disease in normal individuals who have never been exposed to tubercle bacilli.

It is probable that immunization through the agency of abortive con-

tact infections is particularly effective in certain age groups. The more prevalent tuberculosis is in a given population, the more numerous are the chances for children to become infected, a fact which was the cause of much mortality among babies in the past. It is known, on the other hand, that severe tuberculosis is rare in children between the ages of five and fifteen, and it seems not impossible that infection contracted during that age period can provide some immunity against later experiences. The great majority of children were exposed to many sources of contagion up to a few decades ago, and those lucky enough to survive may have grown to form a partially immune population.

As in the case of inborn resistance resulting from genetic selection, immunity acquired through abortive infections is only of relative efficacy in man. Although there seems to be no doubt that populations which have been exposed to tuberculosis for many generations in congested cities are usually more resistant to the disease than are those emerging from a farming or nomadic way of life, this resistance is inadequate to protect the individual exposed to the disease under unfavorable living conditions. Thus, tuberculosis has certainly existed for countless generations in the large Chinese cities, and yet it is still today a terrible scourge there among the poor classes. Their long history of contact with the disease fails to express itself in increased resistance, probably on account of their wretched economic status.

The tragedies caused by the two World Wars have demonstrated that hereditary resistance and acquired immunity are to no avail against infection when environmental conditions become too trying. Forms of tuberculosis with a rapid course and without any tendency to healing became within a few months very common in Europe in the wake of food shortages and loss of elementary human comforts. The tuberculosis mortality rates soared to levels even higher than those reached in the 1850's, and they soon reflected differences in the hardships suffered by the various groups of populations. During peacetime in Warsaw, the disease was much less severe among the Jews than among the Christians, and it had remained so during the first World War, although mortality had increased sharply in both groups. Very soon after the beginning of the second World War, however, the relation changed. From 71 per 100,000 in 1938 the tuberculosis death rate among the Jews climbed to 205 in 1940 and 601 in 1942, whereas the respective figures were 186, 377 and 425 for the Christians. The resistance acquired during centuries

of life in the ghettos proved of little help to the persecuted Jew when his tragic load of ordeals became too heavy.

It is not only under conditions of extreme privations that disturbances of the social fabric can bring about a recrudescence of tuberculosis. Even in England the mortality rate began to increase immediately after the onset of the first World War and it remained high until 1919. An appreciable increase, although less marked and of shorter duration, was also observed during the second World War.* Practically everywhere in Europe, the tuberculosis mortality rate resumed its downward course as soon as social conditions became more normal, or stabilized, at the end of the two conflicts.

These facts make it clear that the environment is of paramount importance to the problem of tuberculosis. And indeed, the tuberculosis epidemic of the 19th century in Europe reached its greatest destructiveness during the first period of industrialization when the economic status of the labor classes was at its lowest, whereas mortality began to decrease concomitantly with the improvement in the general standard of living. At the present time, the disease is more prevalent and more severe among the poor than in the economically favored classes in highly industrialized countries. But universal agreement on the thesis that there exists a correlation between standard of living and resistance to tuberculosis leaves room for many divergent views as to the specific manner in which one affects the other.

Improved standard of living usually means better housing, and chances of infection are decreased by life in less crowded, more airy and sunnier rooms. Even today the relation between the density of population in homes and factories and the prevalence of tuberculosis is still in evidence. A recent survey of the shoe trade in England, for example, revealed that the percentage incidence of tuberculosis increases directly with the number of workers in the plant. A similar relation had been found in cattle years ago; the larger the number of animals per barn, the more likely they are to contract tuberculosis.

More or less simultaneously with improved housing, there began during the second part of the 19th century a crusade for more sanitary living conditions that certainly contributed also to minimize the spread of infected particles. Education made spitting in public places a manifestation of bad taste, sneezing in somebody's face an anti-social act.

* A curve of mortality rates illustrating this statement is presented in the following article. The Tubercle Bacillus and Tuberculosis by R. J. Dubos, American Scientist, July 1949, page 357.

Personal cleanliness became almost a duty, and access to fresh air and sunshine, everybody's right. It is this crusade for sanitation, as we shall see, which has progressively evolved into the systematic sophisticated anti-tuberculosis campaigns of the recent decades with surveys for the detection of active cases, tracing of contacts, segregation of persons with positive sputa, etc. Wherever it has been possible to carry out the war against the spread of bacilli with sufficient thoroughness, the infection rate has been brought down to a very low level. It is unfortunately true that only few communities can afford to carry out adequate public health programs. Nevertheless, there is no doubt that social awareness and public health measures are decreasing the frequency of contact with persons expectorating large numbers of bacilli.

Despite the effectiveness of anti-tuberculosis campaigns in checking the spread of bacilli, the largest part of the population eventually becomes infected, even in communities enjoying a highly developed public health program. This is shown by the fact that most adults—from 50 to 90 per cent—become tuberculin positive* even when they have never shown any evidence of clinical tuberculosis. Furthermore, unsuspected tuberculous lesions—healed or in the active state—can often be found in the body of persons dead of causes other than tuberculosis and who were unaware of being affected by this disease. The reason why mortality rates have been decreasing so much faster than infection rates is not entirely clear. It is possible that under the normal conditions of modern civilized life, most particles of infected sputum or dust that reach an individual contain so few active bacilli that they can produce only abortive infections. It is also probable that the susceptibility of any given individual to infection varies markedly from one time to another, and that the recipient of an infective dose must be in a receptive state for infection to "take" and to cause a progressive disease.

All these considerations make it imperative to inquire into the mechanisms by which physiological state controls resistance to infection.

From time immemorial, clinicians have emphasized the importance of the patient's nutritional state for his ability to resist tuberculosis. Historical and epidemiological evidence also speaks clearly in favor of this view, for there is no doubt that tuberculosis is always more prevalent

* The conversion from the tuberculin negative to the tuberculin positive state is evidence that tubercle bacilli have multiplied to an appreciable extent in the body of the individual concerned—whether or not this multiplication expresses itself by signs or symptoms of disease. Moreover, there is much reason to believe that the persistence of the tuberculin positive state depends either upon the persistence of living bacilli in some part of the body, or upon new contacts with virulent bacilli.

and more severe in areas or social situations where the diet is deficient in "high class" foods. Although it is obvious that inadequate diets are not the only way in which low economic status favors the spread of tuberculosis, there are a few cases where it seems possible to dissociate the effects of bad nutrition from those of the other unsanitary living conditions resulting from poverty.

For example, a striking relation has been observed between diets and the physique and health of two African tribes, the Masai and Akikuyu, both of which live in a primitive state. At the time of a survey made in 1931, the diet of the former tribe was found to consist chiefly of milk, meat and raw blood, whereas cereals supplemented with some roots and fruits were the only foods of the latter tribe. Marked differences were found in the incidence of disease in the two tribes, pulmonary phthisis being in particular many times more prevalent among the vegetarian Akikuyu than among the meat eating Masai.

The course of tuberculosis in Denmark between 1914 and 1918 presents a case where nutrition appears to have been the only, or at least, the preponderant factor in aggravating tuberculosis. The tuberculosis mortality in Denmark, which had been decreasing at a steady rate since at least 1900, showed a marked increase during the first World War between 1915 and 1917. Then the increase stopped, and the curve in mortality resumed its downward trend even before the end of the War. Denmark was not occupied during the first World War; did not take part in the conflict; and suffered no obvious social disturbance that could account for the increase in tuberculosis between 1915 and 1917. It is known, however, that during that period enormous amounts of meat and dairy products were exported to England and that the yearly consumption of meat per individual in Denmark fell sharply. After 1917 submarine warfare interrupted the export trade, and it seems that the reversal of the trend in tuberculosis mortality occurred concomitantly with the return to more normal nutrition. There is some evidence that a similar situation occurred in certain parts of France during World War II. The consumption of meat and dairy products in Normandy and Brittany increased when difficulties of exchange interfered with the shipment of these foodstuffs to other parts of France. At the same time, the tuberculosis mortality decreased in these two provinces while it reached extremely high levels in Paris and many large cities, as well as in certain other regions with deficient food production. In England,

statistical surveys have also revealed an astonishing correlation between consumption of "animal proteins" and tuberculosis mortality. It must be emphasized again that, suggestive as they are, these correlations are not entirely convincing since the decrease in availability of meat and dairy products usually coincides with other disturbances in the social fabric. Moreover, none of the observations made thus far reveal anything of the nature of the particular constituents of the food that affect resistance to tuberculosis.

It has been widely assumed that animal and dairy products exert a beneficial effect by virtue of their protein content, but it is equally plausible that they supply other constituents which are deficient in plant foodstuffs. In reality, and despite the countless pages that have been written on the effect of nutrition on tuberculosis, no knowledge whatever is available of the components of the diet involved in this effect, or of the mechanism by which the state of nutrition affects the course of disease. So complete is our ignorance of the subject that it is not even known whether the nutritional factors that promote resistance to tuberculosis react directly with the tubercle bacilli or their toxin, or act indirectly by increasing either general physiological well-being, or some specific defense and repair mechanisms of the body. There have been a few timid attempts to determine the effect of *known* nutritional factors on infection. But the results have been equivocal and indeed it is unlikely that this approach will yield the solution of the problem. For it would be a miracle if the food components that have been found of significance in the control of nutritional conditions would prove to be also the ones that affect the course of tuberculosis. In order to illustrate the problem by an analogy, it need only be pointed out that the anti-pernicious anemia factor could never have been discovered by testing indiscriminantly the various substances known at the time to be concerned in deficiency diseases. The relation of nutrition to tuberculosis deserves more systematic and especially more imaginative study than it has received heretofore.

Among other aspects of the standard of living that have been invoked to account for the decrease in tuberculosis after 1850, particular mention must be made of the shortening of working hours, and of the decrease in the amount of physical effort exacted from the labor classes. Coincident with this social change was an increasing awareness by clinicians of the importance of rest in the treatment of the disease. In this case

again, universal agreement on the very general terms of the problem is not sufficient to prevent much controversy as to the specific manner in which rest must be practiced, a fact which is not surprising when one realizes that the word rest is used in many different connotations. It is sufficient to recall that, ever since Sydenham and up to a very few decades ago, experienced physicians have prescribed *rest* in the form of horseback riding for many hours every day, for many weeks in succession; today, *rest* means as complete immobility as possible in the recumbent position for months or years. The modern physician speaks also of putting the lungs *at rest* by artificial pneumothorax or other surgical procedures. And throughout recorded history it has been advocated that the mind of the tuberculous patient be put *at rest* by the avoidance of painful emotions or of financial worries, and by sending him to live in pleasant surroundings. Thus, the word *rest* is used to express a whole range of meanings extending from the grossest physical concepts to the most subtle psychic influences. No one knows why and how rest exerts its beneficial effects—whether it favors the healing process around lesions already existant, or increases resistance to the invasion of areas of the body as yet unaffected. But *rest* there must be, mechanical, physiological and psychological.

The use of the word rest in so many different connotations symbolises the belief that resistance to tuberculosis is determined by factors of the host that can be influenced by the proper way of life. Although the different physical, physiological and psychic factors may each influence the response of the patient to infection by means of unrelated processes, it is also possible that all of them operate indirectly through one or a very few common mechanisms, for example, through the hormonal systems that control tissue reactions. Recent studies on the dramatic effects exerted by the components of the anterior pituitary—adrenal system (ACTH and cortisone) on the course of tuberculosis illustrate one mechanism by which many types of stresses can have far-reaching effects on infectious disease. It is not to be doubted that practices developed empirically, and often conflicting in appearance, will be reconciled as knowledge increases of the complex interplay between psyche and soma.

Certain phenomena of epidemiology are in agreement with the view that general physiological factors—other than immunological processes—exert a profound effect on resistance to tuberculosis. Even at a time when tuberculous infection was well nigh universal, the mortality caused by

TABLE II — MORTALITY RATES OF TUBERCULOSIS, PNEUMONIA AND BRONCHITIS, DIARRHEA AND ENTERITIS, BY AGE GROUPS, IN THE UNITED STATES, IN 1900 AND 1940*

Age Group	1900			1940		
	Tuberculosis	*Pneumonia and Bronchitis*	*Diarrhea and Enteritis*	*Tuberculosis*	*Pneumonia and Bronchitis*	*Diarrhea and Enteritis*
5	146.1	862.7	1175.1	14.6	188.4	102.4
5-14	36.2	39.7	8.8	5.5	6.9	0.9
15-24	205.7	47.1	5.7	38.2	8.8	0.7
25-34	294.3	74.4	7.5	56.3	13.4	1.0
35-44	253.6	109.2	1.05	59.4	22.8	1.6
45-54	215.6	169.3	18.6	66.3	42.9	1.9
55-64	223.0	331.2	49.3	76.1	83.0	3.4
64-74	256.1	683.1	130.4	80.8	187.4	7.0
75+	269.2	1666.7	365.8	77.8	691.8	29.8

* Data kindly supplied by Dr. A. E. Cohn and Miss Claire Lingg.

the disease in children of the age group from five to fifteen was—as already mentioned—much lower than that observed among younger or older individuals. Many reasons have been invoked to account for this "golden age of tuberculosis." Suffice it to emphasize here that the phenomenon must be the expression of some general biological law since the high resistance of the 5-15 age group to infection is not peculiar to tuberculosis. As shown in Table II it applies to bronchitis and pneumonia as well as to the ill-defined conditions entered on death certificates under the names of diarrhea and enteritis. Many other examples could be quoted, but none is as striking as tuberculosis. Of particular interest is the fact that dependence of susceptibility on age was already obvious in 1900, at a time when infection was wellnigh universal. Although immense numbers of babies and young adults were then dying of tuberculosis, most children of school age escaped progressive disease despite constant and heavy exposure to the bacilli. The changes in the prevalence of tuberculosis during the past five decades have not altered this relation between age and susceptibility to disease (Tables II and III). A recent analysis has brought the phenomenon into sharp relief by correlating mortality rates with incidence of infection (determined by the tuber-

TABLE III—AGE-SPECIFIC DEATH RATES OF TUBERCULOSIS (ALL FORMS) PER 100,000 ESTIMATED POPULATION*

Age	1940	1939	1938	1935	1930	1925	1920	1915	1910	1900
All Ages	45.9	47.1	49.1	55.1	71.1	84.8	113.1	140.1	153.8	194.4
Under 1 year	24.6	26.6	28.4	35.5	51.6	69.7	106.5	168.6	212.9	311.6
1-4 years	12.3	13.6	15.6	16.3	25.9	30.3	45.4	68.0	84.6	101.8
5-14 years	5.5	6.0	6.5	7.9	11.9	14.8	22.4	26.9	29.7	36.2
15-24 years	38.2	39.4	43.2	48.9	77.3	101.7	136.1	146.1	152.0	205.7
25.34 years	56.3	58.7	62.9	74.1	102.8	122.5	164.9	198.0	217.6	294.3
35.44 years	59.4	60.6	64.4	75.5	92.4	110.6	147.4	196.9	214.9	253.6
45.54 years	66.3	69.7	69.1	77.9	93.2	106.4	137.2	176.8	188.1	215.6
55-64 years	76.1	75.4	78.2	83.8	97.0	108.2	141.3	177.0	192.9	223.0
65-74 years	80.8	82.3	83.0	90.5	111.7	132.7	163.8	187.8	203.5	256.1
75 years and over	77.8	82.5	80.1	96.4	110.0	122.1	154.2	160.5	179.0	169.2

* Data taken from Vital Statistics, U. S. Department of Commerce, 16, 1942, No. 7, p. 29.

culin test) in different age groups. As shown in Table IV which was prepared from data obtained some 10 years ago, tuberculosis was then —as in 1900—most fatal when contracted during the very first years of life. The mortality was at its lowest point from age 5 until puberty, in spite of increased chances of infection. It increased again at the time of puberty and remained high until death. There could not be more telling evidence that infection and disease are not synonymous.

All attempts to study the mechanisms by which selective breeding, abortive infections, nutrition, and physiological factors modify resistance to tuberculosis, are handicapped by our ignorance of many fundamental aspects of the pathogenesis of the disease. This is particularly true of caseation, a peculiar form of tissue necrosis which constitutes one of the most characteristic findings in tuberculosis. The necrotic tissue that has caseated instead of undergoing ordinary autolysis is slow to resolve and may persist for periods of years, providing a peculiar environment for the tubercle bacilli. As long as the caseous lesion remains closed, the bacilli that it contains stop multiplying and even slowly decrease in numbers, but some of them survive for months or years, even long after apparent clinical recovery has taken place. This fact is of enormous

TABLE IV — MORTALITY FROM TUBERCULOSIS AT DIFFERENT AGE PERIODS IN THE GENERAL POPULATION AND IN THE INFECTED PORTION OF THE POPULATION**
(U. S. Registration Area, 1940)

Age	*Total Deaths from Tuber-culosis*	*Estimated Per Cent infected**	*Deaths from Tuberculosis per 100,000 Persons of each age group*	*Deaths from Tuberculosis per 100,000 estimated infected persons of each age group*
0- 1	496	0.5	24.0	4,920
1- 4	1047	10	12.3	123
5- 9	469	25	4.4	18
10-14	775	35	6.6	19
15-19	3357	45	27.4	61
20-24	5752	55	49.6	90
25-29	6243	65	56.3	87
30-34	5773	75	56.4	75
35-39	5448	85	57.1	67
40-44	5438	90	61.9	69
45-49	5222	95	63.3	66
50-54	5058	95	69.7	73
55-59	4409	95	75.4	79
60-64	3641	95	77.0	81
65-69	2975	95	78.2	82
70-74	2179	95	84.8	89
75 over	2057	95	77.8	82

* Estimated from tuberculin surveys.
** Reprinted from Arnold R. Rich, *The Pathogenesis of Tuberculosis,* Charles Thomas, Springfield, 1944, p. 217.

importance to the infected individual and to the community in which he lives. For many ill-defined circumstances which result in the re-penetration of body fluids into the caseous area, or in the opening of the latter into a bronchus or a blood vessel, change the characteristics of the lesion in such a manner that the surviving bacilli start multiplying again and bring about recurrences and spreads of disease. On the other hand, the prolonged survival of a few bacilli within the caseous area is of epidemiological significance by maintaining in the community reservoirs of infection that keep the epidemic smoldering. The importance of these

facts has been repeatedly pointed out by clinicians and epidemiologists and yet there is no understanding of the mechanisms that result in the production of caseous matter, or in the "softening" of caseous areas. Here is a vast field of inquiry that certainly cannot be solved by the simple bacteriological public health approach and which requires instead an integration of immunological with biochemical and physiological analysis.

Many will probably wonder whether the biological aspects of tuberculosis constitute a worthwhile subject of study at the present time since higher living standards and decreased chances of infection have gone far toward robbing the disease of its social importance and since the present medical procedures have greatly improved the chances of survival of the tuberculous patient. Unfortunately, the situation is not as satisfactory as the decline in death rates would lead one to believe. There are close to 1,000,000 individuals in the United States alone and probably 100,000,000 in the world, who harbor living virulent tubercle bacilli. Complete eradication of the disease is therefore an impossibility for many decades. The varied programs that have been organized for the detection of active cases will bring to medical attention more and more patients in the early phase of their disease, and thus improve their chance of recovery. But disturbing problems are already becoming apparent. To what extent will society be willing—and able—to provide hospital or sanatorium treatment for all those who are "infected," but only potentially sick? The economic cost would be staggering, certainly exceeding a billion dollars yearly for the United States alone. And how many of the individuals found to have tuberculous infection, but otherwise feeling no unpleasant symptoms, will accept the idea of removing themselves from normal life for months or a year, merely as an insurance against the threat of disease? As is well known, in only a very small percentage of persons does tuberculous infection evolve into incapacitating illness and there is at the present time no technique and no knowledge to determine which of the infected individuals are threatened with progressive disease.

However useful in specialized cases, vaccination, anti-microbial drug therapy, or surgical intervention cannot possibly bring the solution to the *social* problem of tuberculosis. And yet it is certain that a solution can be found. For it must never be forgotten that tuberculosis is not an inevitable accompaniment of human life as is shown by the facts that it has long remained practically non-existent in many primitive societies

and that it is disappearing as an important medical problem from some limited sections of the most highly evolved modern communities. It is only through gross errors in social organization, and mismanagement of individual life, that tuberculosis could reach the catastrophic levels that prevailed in Europe and North America during the 19th century, and that still prevail in Asia and much of South America today.

Fortunately, tuberculosis can be attacked along two independent lines—by decreasing the chances for infection, and by rendering man more resistant to the damage caused by tubercle bacilli. It is only through this dual approach that the anti-tuberculosis movement can be seen in its proper perspective—which is not merely a medical perspective but one in which the historical and social backgrounds loom very large. True enough, the many factors that have contributed to the decline of tuberculosis in the Western World began to operate long before the anti-tuberculosis movement had acquired momentum, indeed even before the germ theory of disease had gained widespread acceptance. But it must be realized that concern with public sanitation antedated the germ theory. The campaign to eliminate filth and squalor from society, and to bring pure air, pure water, pure food and healthy living conditions to the multitudes, originated with the great humanitarians of the early nineteenth century. The crusade for outdoor life, open windows, cleanliness of body and habits probably played a part larger than is usually realized in decreasing the spread of infection. Certainly the germ theory of disease helped in making more pointed and more effective the policies of public hygiene. But it was the "sanitary awakening" that prepared the way for the new health movement and did much of the work usually credited to the bacteriological doctrine. It matters little whether crowding, promiscuous spitting, dark airless rooms, and other unsanitary aspects of life in society are condemned in the name of human decency, sanitation or the germ theory. The practical effects are the same in bringing about a way of life that minimizes the spread of certain infectious agents and of tubercle bacilli in particular. Thus, one can recognize an unbroken continuity of public health work since the beginning of the sanitary reforms. The anti-tuberculosis movement took up and carried further the torch first lighted by the public-minded physicians and laymen of the 1830's.

In addition, the anti-tuberculosis movement elevated the medical education of the public to a more sophisticated level. It conveyed the knowl-

edge that disease can exist and can be detected long before the patient becomes aware of symptoms. It taught that diagnosis in the earliest possible—asymptomatic—phase of tuberculosis is of paramount importance, both for the individual patient, since it increases his chances of complete recovery, and for the community, since it helps in finding the source and in breaking the chain of infection. The tuberculous patient has been indoctrinated in the belief that it is *his* responsibility to take measures that will minimize the spread of bacilli—either by accepting segregation in a sanatorium or by learning to behave in such a manner that he does not contaminate his surroundings.

Whereas the germ theory of disease gave a rational basis to the empirical sanitary measures initiated in the 1830's and thus led to a more effective fight against the spread of bacilli, no similar body of scientific doctrine has come to guide the anti-tuberculosis movement in its efforts to render man more resistant to infection. There is as yet no clear understanding of the mechanisms by which the body can ward off infection or progressive disease, and there is no way of measuring either inborn resistance or acquired immunity. This ignorance greatly handicaps all efforts to develop methods for producing a truly effective specific immunity. At first sight, the situation appears more satisfactory with reference to the medical techniques used in the management of the tuberculous patient since the practices codified in sanatorium life—whether carried out in a city hospital, or in a secluded country resort—are unquestionably of benefit both to the patient and to society. But it is not unlikely that the same results could be obtained with more certainty, less time, and at lower cost of human and economic values, if precise knowledge were available of the factors that affect the course of tuberculosis. At the present time, advocates of "healthy living" have little to add to the teachings of common sense preached by the health crusaders of the past century. Even more than in the case of immunological processes, the precise nature of the physiological mechanisms that control resistance to tuberculosis is entirely unknown, and little more than lip service is paid to the need for investigating them. And yet, it is likely that we are reaching the point of diminishing return in what can be expected from the application of present knowledge. There is more to the problem of nutrition than prescribing three square meals a day, and rest must be defined in terms other than the number of hours spent in bed.

Some fifty years ago men of vision and of good will—physicians and

laymen—realized that tuberculosis could not be conquered by the conventional medical philosophy of the time. Their efforts culminated in the educational program that enlisted the general public as an understanding and creative participant in the war against contagion. There is needed today, a re-awakening of the pioneering spirit that brought about first the sanitary revolution, and later the anti-tuberculosis campaigns. Once more it becomes urgent to force upon social consciousness the realization that progress cannot depend only on doing more and more of what has proven profitable in the past.

A new educational process is needed to make the public, and those responsible for the administration of scientific programs, become aware of the fact that research should not be limited to working out more and more details of established principles—to gilding yesterday's lilies. The important advances are likely to come from the workers who stray from the obvious paths and venture into unexplored areas. But it is not easy to integrate these temperamental trail blazers into the rigid and cumbersome structure of large educational or research institutions and of governmental bodies. For this reason voluntary and unofficial agencies have an important role to play in searching, recognizing and encouraging unorthodox approaches to the study of tuberculosis. It took much boldness of spirit to establish in the 1900's the new philosophy that permitted physicians and the public to work together. It will take much imagination and vision to foster the development of new research concepts, of new points of view, within the ever-growing rigidity of our social framework. Needless to say, we must keep on exploiting the techniques of tuberculosis control that are the direct expressions of the germ theory of disease. But we must realize that the complete elimination of tubercle bacilli, however desirable a goal, will not be achieved for a long time to come—if ever. Since tubercle bacilli are likely to remain widespread, it becomes imperative to investigate the human and environmental factors that determine resistance to infection. The final step in the conquest of tuberculosis may well depend upon knowledge of the factors that prevent infection from manifesting itself in the form of destructive and progressive disease.