THE PREVENTION OF TUBERCULOSIS

ARVID WALLGREN

With regard to tuberculous infection we may divide the life of a human being into three periods: 1. The pre-infection period; 2. the incubation period; and 3. the period of latency and of manifest tuberculous disease. The end of the pre-infection period is determined by the occurrence of the first infection. The end of the incubation period is marked by the establishment of tuberculin sensitivity.

The prophylactic measures vary during these three periods. The pre-infection period is the period of choice of specific vaccination. An already infected child has acquired by natural virulent infection a degree of specific immunity that is far stronger than the artificial immunity which is acquired by vaccination. Vaccination cannot prevent tuberculosis infection, but it diminishes the risk of virulent disease after the first infection, and may, therefore, be called *specific disposition prophylaxis*.

During the same period tuberculosis is prevented by protecting the child against infection. This we call *infection prophylaxis*. There is reason to believe that the period of infection prophylaxis may with benefit be extended even to the incubation period. It may be of prophylactic value to prevent new exogenous infections during this pre-immune period. The value of adopting special measures subsequently in order to prevent the common exogenous re-infections in allergic subjects is, according to my experience and opinion, questionable. For my part, I have never seen a case of clinical tuberculosis the manifestation of which could be traced to a new exogenous infection. On the other hand, I have followed-up thousands of tuberculin-positive children exposed to exogenous re-infections without being able to note any bad effect on the children's health.

During the third period, after the tuberculin sensitivity has been established, we try to prevent the manifestation of tuberculous disease by strengthening the natural resistance and general health of those infected. This is the period of *non-specific disposition prophylaxis*. This form of prophylaxis need not be confined to those who are tuberculin-positive. It may be extended even to uninfected sub-

jects. Thus, the non-specific disposition prophylaxis, theoretically speaking, begins at birth and ends with the death of the individual.

It is obvious that prophylactic measures are of little value once tuberculous diseases are manifested. This should be the period of treatment.

With this summary of the different measures that have to be adopted and their periods of choice during the course of tuberculous infection, I pass over to a more detailed report of the manner in which these measures are carried out in Gothenburg, a Swedish city with 275,000 inhabitants.

The prophylaxis of tuberculosis has two objects: Prevention of tuberculous infection, and prevention of tuberculous disease.

The *prevention of tuberculous infection* must proceed along two different lines, according to the nature of the source of infection to be eliminated, the tuberculous human being or the tuberculous cow.

It is well known that, with but few exceptions, tuberculous infants and small children receive their infection from a consumptive member of the family. Thus, attention should be paid especially to the possibilities of intra-familial infection at this early age. To be in a position to prevent intra-familial infection it is necessary that the source of contagion should be discovered in time, before the child is infected. It goes without saying that in this connection it is of great importance that every case of tuberculosis be duly reported. From my hospital every child treated for tuberculosis is immediately reported to the dispensary. After such notification the social worker at the dispensary visits the child's home. She inquires about the relatives and induces those in the environment of the child to be examined by the dispensary medical staff.

All infants and children attending any of the community's social institutions or schools are tested with tuberculin, and the positive reactors together with their family-members are sent to the dispensary for further examination. In this way new sources of infection are very often detected.

If pulmonary tuberculosis has been diagnosed in a member of a family where there are children, the next step must be to try to prevent the disease from being transferred to the still uninfected children. At the dispensary a record is kept of all expected children and those born in tuberculous families. In the case of each child the precautionary measures which are considered necessary are taken.

The nature of the measure will depend on the degree of infectivity of the affected member of the family, the condition of the home, th ability and the prospects of the parents to take proper care of the child, etc.

If the consumptive is living at home and the child is not yet born, the parents are induced to give their consent to the child being taken care of immediately after birth. According to our Laws on the Welfare of Children, parents cannot ignore such measures. Every child that is threatened with ill-health by living in its home has to be taken care of by the state or the community. It is very seldom that we are obliged to have recourse to this law; with very few exceptions the parents voluntarily give their consent to the infection-prophylaxis recommended.

If the consumptive has been living in a home where there are infants or children who have thus already been exposed to the risk of contagion, the sick person is given proper care at the Hospital for Consumptives and the children are tested with tuberculin. The negative reactors are tested six weeks after the last exposure to infection, or earlier if they show fever or other morbid symptoms. If they are still tuberculin-negative in six weeks after the last exposure they are regarded as uninfected.

Such children, who are not actually infected but are in danger of becoming so in tuberculous homes, are, through the machinery of the tuberculosis dispensary, taken care of in a tuberculous-free environment. In Sweden this care is given in two different ways. In the most southerly parts of the country they have tried the French system of boarding out the children in healthy families. In Gothenburg we take care of the infants at a Children's Home. In my opinion a well-managed institution of this kind is to be preferred to a private home. The parents themselves would rather send their children to such an institution than, as foster-children, to a private family. This minor point is of importance when we have to obtain the consent of the parents for removal of the child.

In Gothenburg we have two such Infants' Homes in which we admit children who are in danger of being infected. These Infants' Homes belong to private societies but are supported by the community. Our National Anti-Tuberculosis League pays for the children at these homes. The institutions are supervised by well-trained pediatricians, and the infants get breast-milk, at least during their first 3 or 4 months of life. The breast-milk, which I regard

as necessary diet in such an institution, is partly received from wet-nurses, partly bought from mothers who have a surplus of breast-milk and belong to the infants' welfare centers.

The effects of such an exposure prophylaxis with respect to protection against tuberculosis are absolutely good. The children remain uninfected as long as they are cared for in this way. A very important question is how long the child should be kept away from its home. The length of the isolation period depends on a number of different factors, not the least important of which are the condition of the child's home, the degree of infectivity of the sick parent or sibling, and the desire and ability of the parents to understand correctly the danger of contagion and to lessen its degree. The duration of the period of isolation will, therefore, vary from case to case. Frequently this problem solves itself in that the sick individual dies or is admitted to a hospital. The older the child, the less dangerous is the primary infection as a rule. Considered solely from the point of view of mortality, it may be said that generally the greatest danger is past when the child has reached the age of 3 or 4 years.

Infants, however, are not only in danger of contracting tuberculosis from a consumptive member of the family; even infectious persons outside the family circle may be a danger to the child. It is undoubtedly a very important task to educate the parents and to instruct them to protect the child from tuberculous infection by preventing them from intercourse with tuberculous nurses and maids, with casual tuberculous visitors, or with consumptives living in the same house. This we try to obtain by means of an intensive scheme of instruction and propaganda. I cannot here enter into detail as to how this is accomplished, but I may mention lectures, pamphlets, newspaper articles, films, broadcasting, teaching in schools, etc., as parts of the program. In this connection I cannot refrain from emphasizing one very important point, viz., the necessity of cooperation with the lung specialist in explaining to the consumptive what a danger he himself may constitute to non-infected persons, especially infants and small children. In this respect it is better from the point of view of infection-prophylaxis that every consumptive, whether he has had any tubercle bacilli in the sputum or not, distinctly realize that he is to be regarded as a potential danger to infants. Nowadays, adults with pulmonary tuberculosis too frequently stifle their conscience by obtaining a doctor's certificate show-

ing that they, at a certain time of examination, have been found free from tubercle bacilli.

The other source of tuberculous infection is the tuberculous cow. In my sphere of activity practically no bovine tuberculosis occurs and, therefore, my experience with this type of disease is very limited. Our bacteriologist, Dr. Wassén, has typed the bacilli of 705 cases of tuberculosis in Gothenburg and found that only 18 were of bovine origin. Probably all of them acquired the infection during summer vacation periods in the country. Twelve of the cases had tuberculous cervical lymphadenitis.

The reason why bovine tuberculosis is very unusual in Gothenburg, but on the other hand fairly common in the country, is due to the manner in which the milk is treated before it reaches the consumer. In Sweden it is prescribed by law that all milk sold in towns must be pasteurized. In the country it is generally taken unboiled and raw, at least by children above infant age. This difference between rural and urban districts with respect to the incidence of bovine tuberculosis and the method of treating the milk before consumption, indicates the type of prophylaxis required. Until bovine tuberculosis is eradicated, so long as milk from tuberculous cows is sold and used, tuberculin-negative children should not be fed on unpasteurized or unboiled milk. By means of a vigorous campaign carried out in Sweden against bovine tuberculosis we hope that more and more herds of cattle will become tuberculosis-free, whereby the risk of transmitting bovine tuberculosis can also be eliminated in the country.

By preventing tuberculous infection in the manner described, tuberculous disease is also, of course, most effectively prevented. No tuberculous infection, no tuberculosis. The prospect of preventing contact with tubercle bacilli throughout life is at present rather small. In spite of the work expended on infection-prophylaxis during this century, practically everyone will sooner or later be infected. The effect of the infection-prophylaxis has been to postpone the date of primary infection to a higher age. Nowadays, most people in Gothenburg are not infected until after puberty. Most students of tuberculosis consider this result to be a very great gain; others are sceptical as to the advantage of not being infected until adult age.

It is not possible, on the basis of the data supplied so far, to conclude that first infection in adult age is, under all circumstances, to be regarded as more benign than that acquired, for instance, during

school age. To form an opinion as to whether it is advantageous to postpone primary infection until adult age the problem must be viewed from an angle other than the purely medical one. If a school child becomes ill with a primary tuberculosis which entails its absence from school for a month or so, or if it later on develops pleurisy and has to be absent from school for another 3 or 4 months, this loss of time does not mean very much to the child, especially as the illness need not prevent it from continuing its studies while lying in bed. It undoubtedly means much more to an adult if he is compelled to leave off working for an equal length of time. It implies loss of wages, financial difficulties for the family, and possibly loss of situation. From a sociological and economical point of view it must be more advantageous to the individual, *if* he is to be infected at all, that the infection should take place during the primary school years.

The *prophylaxis of tuberculous disease*, the prophylaxis of disposition, should be directed along two lines of attack, depending on whether the purpose is to protect a child already infected from any further consequences of the infection, or to prevent a child not yet infected from developing dangerous symptoms in connection with the manifestation of the primary tuberculous infection. Taking the latter form of prophylaxis first, we may here speak of two different kinds, one non-specific and the other specific.

Non-specific prophylaxis against tuberculous disease comprises all measures which tend to make the clinical-pathological symptoms produced by the first infection as mild as possible. The prophylactic measures against tuberculous infection in earliest infancy will, to a certain extent, also be measures against malignant tuberculous disease: the younger the children are at the time of the primary infection, the more serious are the symptoms as a rule. Postponement of the infection until the child has passed its most susceptible years will, therefore, be an important disposition-prophylactic measure.

Non-specific prophylaxis of disposition includes also all measures directed to the improvement of the general state of health and the child's power of resistance. This we try to fulfill by a strengthening treatment of children in danger of being infected, by improving the home conditions of the family, by aiding the parents to give the child proper diet, by controlling and improving the child's health through the welfare centers and well-managed school hygienic measures, by recreation in summer camps, etc.

Specific prophylaxis of disposition is the attempt to produce an increased resistance to tuberculous disease by means of artificial specific immunity. This tuberculosis vaccination is based on observations made concerning specific immunity after infection. By means of vaccination it is intended to produce the immunizing effect brought about by a spontaneous infection, without exposing the individual to the attendant dangers. The best way of artificially producing an immunizing effect is to imitate as closely as possible the conditions existing in the spontaneous tuberculous infection. Among other things, it must be borne in mind that the immunity cannot be definitely recognized until a positive tuberculin reaction is obtained.

To be approved, a vaccine of this kind should fulfill at least two primary conditions: It should be free from any element of danger, and there should be some proof of its efficacy. Experiments have shown that the vaccine, in order to conform to these two requirements, must be made of avirulent, but living, tubercle bacilli. The prototype of this kind of vaccine is the well-known BCG-vaccine of Calmette and Guérin.

The story of the production of the BCG-vaccine is, no doubt, well known. I shall therefore content myself with mentioning that the vaccine is composed of an originally virulent strain of bovine tubercle bacilli, which by means of certain methods of cultivation has been made very nearly avirulent. By reason of its properties, and judging from the experimental results obtained, it seems to be well worth the extensive experiments that have been carried out on both human beings and lower animals.

As the result of experimental investigations made at different places, the conclusion has, practically unanimously, been reached that animals inoculated with BCG-vaccine are more resistant than unvaccinated control animals. According to experiments performed on man in different countries (France, Norway, Sweden, the United States) it would seem certain that BCG produces an immunizing effect also in man. As to the harmlessness of this vaccine, a careful and critical study of the literature available shows that up to the present not a single one of the millions of children who have been vaccinated has suffered any evident harm from a correctly prepared and correctly employed vaccine. My own experience confirms this view.

I want to stress the following two points as to the effectiveness of the vaccine. 1. A virulent tuberculous infection does not pro-

duce more than a relative immunity, and since the avirulent BCG-infection is surely less immunizing than a virulent one, it cannot, of course, be expected that vaccination will afford absolute protection. That would be to place too great a demand on the vaccine. 2. It should also be clearly understood that a BCG-vaccination cannot protect the individual from secondary or tertiary tuberculous diseases any more than the immunity from a natural spontaneous infection can do so. At best, it can prevent the severest forms of primary tuberculosis.

The extent to which the vaccine protects the child against the dangers of a virulent infection is not known, nor have we any knowledge of the duration of such protection. Under these circumstances we considered it wisest, when starting this campaign, to confine vaccination to those children who were regarded as likely to become exposed to contagion in the near future. This applied to all children of tuberculous parents when the children for some reason or other could not be isolated from the source of infection.

In order to obtain any benefit from vaccination, the child must be free from tuberculosis. We have vaccinated new-born infants and non-exposed children as soon as they have come under our care. Children who have been exposed to possible infection have been vaccinated only in the event of their being found to be tuberculin-negative after a lapse of from six to eight weeks from the date of their last exposure.

Whether the vaccination-immunity is present before the tuberculin test has become positive is as yet unknown. When it comes to the question of deciding when a vaccinated child may be permitted to return to its tuberculous home, it would at all events be safest to assume that the child has acquired this immunity only when it has become tuberculin-sensitive. It is on these principles that we have acted in Gothenburg.

Our technic of the BCG-vaccination has been as follows. After evidence has been obtained by means of tuberculin tests that no virulent infection is present, even after an eventual incubation period has expired, the suitable dose (0.05 mgm.) of vaccine is injected intradermally. This is done into a part of the skin which is relatively well protected, for instance, the front of the upper arm or the region of the scapula. By means of tuberculin tests made six to seven weeks later we ascertain whether allergy has developed; until that has occurred the child is regarded as unvaccinated and unprotected from virulent infection.

From the available very restricted experience one may conclude that the artificial immunity produced by vaccination lasts for several years in general, sometimes for from 5 to 10 years or more. Because only children in tuberculous families have been vaccinated the temporary artificial immunity is usually succeeded by a permanent natural one, produced by a silent virulent infection. A vaccinated child, whose tuberculin sensitivity has worn off, is regarded as unvaccinated; the same dose is injected as in the initial vaccination and the same procedure followed.

The BCG-vaccination in Gothenburg was originally carried out at my hospital, but for the last five years the tuberculosis dispensary has taken charge of the work. The tuberculosis officers or the dispensary nurses have succeeded, with but few exceptions, in inducing the parents to consent to the vaccination. When the parents have been informed of the danger threatening the child at home, and that, for the sake of diminishing this danger, they must either separate the child from the tuberculous member of the family or have it vaccinated, they have, of course, chosen the latter alternative.

Calmette's vaccination must not be regarded as sufficient in itself, but must always be considered as an adjuvant to other prophylactic precautions, of which the separation from the infected person is to be regarded as the essential one. The advantage which a separation can yield the child is also implied in the above method of vaccination. At any rate, the child escaped a virulent infection in the first period of its life. An infant should be isolated from the infectious person at least until it becomes tuberculin-sensitive after vaccination, i.e., for about six or eight weeks. If the child has already been exposed to infection it is separated from the source of infection during the incubation period of the possible infection, i.e., about six weeks; then vaccinated, after which it is again isolated for a further six or eight weeks during the incubation period of the vaccine. Thus such a child is protected from infection for at least three to four months in all. For various reasons it is easier to obtain the consent of the parents to prolong the separation of the child from home once they have become accustomed to the child's absence.

In 1934 I reported the results of the BCG-vaccination carried out in my hospital, and from that communication I will quote some figures. Up to that date, 355 infants had been vaccinated and of these 230 had been exposed to tuberculous infection in their homes for a total number of 5250 exposure-months. At the follow-up

study it was found that only one child had acquired an evident primary tuberculosis and this of a benign type; in 11 cases the hilus shadow was slightly enlarged or suspected to be enlarged; and in 216 children it was quite normal. No child had died from tuberculous disease.

In 1939 the medical staff of the tuberculosis dispensary reported on the result of a new follow-up examination of the vaccinated children. Their number up to the end of the year 1937 was 1069. Every child was tested with tuberculin and x-rayed. It was found that only two cases of transient tuberculous disease had occurred and no deaths had taken place from tuberculosis; whereas among the "control material," which amounts to a very small percentage of the material investigated, there occurred five deaths and a number of cases of tuberculous disease.

The effect of all favorable factors involved in the method of vaccination employed can be seen by comparing the above figures with the conditions which prevailed when this system was not in use in Gothenburg. Deaths from tuberculosis among infants occur as a rule among those in infectious surroundings, and almost every one of those infants that die has been vaccinated. Those children who are infected before the discovery of the source of infection cannot of course be vaccinated and protected and some die from tuberculosis. A prophylactic measure, such as the one described here, even if it were absolutely effective, could not therefore prevent every death from tuberculosis occurring in infancy.

The result of the prophylactic measures introduced in 1927 can be seen from the following figures. In the three 5-year periods immediately preceding 1927 the death rate from tuberculosis among infants was 4.3, 4.2, and 3.4 per thousand, respectively. In 1927, which was a year of transition with only a few children vaccinated, the mortality amounted to 3.9 per thousand. After 1928 it may be considered that the principles advanced here have been strictly applied. During the first 5-year period, 1933–1937, the mortality rate was only 0.5 per thousand. In 1938–1941 it was also 0.5 per thousand. It should be noted that the general tuberculosis death rate, especially from pulmonary tuberculosis, has not shown the same downward tendency. This signifies that the number of the sources of infection has not, broadly speaking, decreased in proportion to the decrease in the number of deaths from tuberculosis in infants.

At all events it must be remembered that the protection afforded by the BCG-vaccination is only relative and is, in addition, of limited duration. It is, therefore, imperative that other precautionary measures against tuberculous contagion should not be neglected.

There are two conditions that favor the development of tuberculous disease in those infected: 1. The lowering of the natural resistance by bad household conditions, unhygienic living, emaciation, etc.; 2. Acute infections, which may reduce the subjects' power of resistance. The disposition prophylaxis may thus be divided into general and anti-infectious measures.

The general measures are intended to eliminate everything unnatural, unhygienic, and unwholesome in the child's diet, care, mode of living, and development. To enter into details would be superfluous. I would, however, like to call attention to the importance of preventing rickets and intestinal disorders in infants and small children. Both these affections undermine the child's power of resistance and tend to cause an acquired tuberculous infection to pursue a malignant course. In this connection we may mention that more than two-thirds of all infants in Gothenburg are supervised by the infant welfare centers, that they are with but few exceptions fed on breast-milk, and that all infants and small children are given cod-liver oil or cod-liver oil preparations in winter time. The general infant mortality rate during the last 5-year period has amounted to only 28.9 per thousand.

Small children and school children who are in need of it are to a certain extent given an annual recreation period in the country, at the seaside, etc. School children in delicate health are taught in special classes, so-called "health classes" or "open-air classes," or are sent to the open-air boarding school of the community, situated in the country, an hour's drive from Gothenburg. Much has been done for the improvement of the general standard of living, especially for families with many children. Special blocks of flats have been built, supported by state and community, so called "sun-dwellings," where most of these families live. For the working classes the single-house movement has had great success and in the suburbs of Gothenburg we have colonies of one-family houses. We have very little unemployment in our country and, generally speaking, the standard of living of the laboring class is rather high.

It is generally known that certain acute infections may bring about a flaring-up of a previously latent tuberculous infection.

First, mention should be made of measles and influenza in this connection, and second, whooping-cough. These, as in fact other acute infections, should as far as possible be prevented in children infected with tuberculosis, especially when the infection is still fresh. As regards measles, we are fortunate in having an effective prophylactic remedy in convalescent serum, which has been of great importance to our children infected with measles and tuberculosis. With regard to influenza and whooping-cough, we have to content ourselves by carrying out as strict an isolation as possible, in the latter affection also attempting to prevent the disease or to alleviate its course by means of prophylactic vaccine therapy.

In combating tuberculosis we lay the greatest stress on prophylaxis. As prophylaxis, in a broader sense, we may include even the early treatment of fresh primary tuberculosis. In treating and curing these diseases as rapidly as possible we hope to prevent the occurrence of the more malignant tertiary diseases in later years. The adage: "An ounce of prevention is worth more than a pound of treatment" has been our guide in combating tuberculosis among children in Gothenburg.