CURRENT PROBLEMS IN THE TUBERCULOSIS OF CHILDHOOD.

Infection, Diathesis, Artificial Pneumothorax, Preventive Inoculation.

BY

ALAN MONCRIEFF, M.D., M.R.C.P. London,
(Medical Registrar, The Middlesex Hospital.)

It is a striking fact that tuberculous infection in infancy and childhood has not diminished in proportion to that of the adult. Aschoff,⁽⁴⁾ quoting Gottstein, has particularly emphasised this, and he points out that there are still many problems with regard to the pathogenesis of phthisis yet to be solved. A review of certain views on these problems in the light of recent contributions to their study has been undertaken here almost entirely with regard to lung infections.

ROUTES OF INFECTION.

As far as intra-thoracic tuberculosis in children is concerned the human tubercle bacillus is generally accepted as the important factor, and some authors even go so far as to extend this so as to cover infection elsewhere, largely denying that the bovine bacillus plays the part commonly assigned to it.

A. S. Griffiths⁽¹⁷⁾ collected the results of several investigators on this point and added his own experience as to the type of bacillus isolated from the sputum of phthisical patients, with the result that in 938 cases the bovine bacillus occurred alone in three cases, and a mixed infection of the human and bovine types in another three cases. Calmette⁽⁹⁾ has likewise collected the results of 27 investigators, and of 832 cases in only three were bovine bacilli found alone. In 18 cases of primary bronchial gland tuberculosis the human bacillus alone was isolated in 17 cases as reported by Cobbett.⁽¹²⁾ Another interesting point in favour of the human origin of the bacillus in pulmonary tuberculosis is the fact that in Japan cow's milk is not employed at all in the feeding of infants, and yet the morbidity and mortality rates of pulmonary tuberculosis are quite as high there as in this country. [Kitasato, quoted by Calmette.⁽⁹⁾] A similar state of affairs is said to exist in Turkey and Greenland.

With regard to the port of entry of the bacillus there are, broadly speaking, three views. Calmette and his school, following von Behring, insist on the importance of the intestinal route. According to this view bacilli are swallowed, pass through the mucous membrane of the intestines

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without leaving any trace, and may either pass up lymphatic channels to the thorax or enter the blood stream and be deposited in the lungs. Calmette's work in which he fed animals on pigmented food and found the pigment in the thoracic glands has, however, been somewhat discredited, and the "intestinal route" has not many supporters at the present time outside France. That infection of the lungs is ærogenous in nature is probably the most widely accepted view. Kuss, H. Albretch, and, later, Ghon, have done a great deal of work on this. Ghon⁽¹⁶⁾ in particular has described the primary lung focus in tuberculosis in children. Out of 184 autopsies carried out by himself he was able in 95% of cases to find a small focus in the lung, usually situated just under the pleura, while the glands draining this area of the lung were enlarged and infected. A small bronchus could usually be traced out to this focus which occurred more frequently in the right than in the left lung, and the changes in the lung were generally more advanced than in the glands; all points in favour of an ærogenous infection. Aschoff⁽⁴⁾ has recently called attention to the supreme importance of Ghon's work. While the presence of a primary lung focus is not admitted by many workers, it is generally agreed that the first obvious effect of a tuberculous infection of the lungs is an enlargement of the glands in the neighbourhood of the hilus. This is the "adenopathie-tracheobronchique" of the French and "bronchial-drusentuberkulose" of the German authors for which we have no comprehensive term in English. The third possible route of infection is that in which the tubercle bacillus gains an entry through the lymphatic ring of the pharynx, *via* the tonsils or adenoids, and tracks down through the cervical lymphatic system to the thorax. Cobbett⁽¹²⁾ concludes that "tubercle bacilli do occasionally pass through the intact cervical glands when animals are made to swallow very large quantities of these micro-organisms, but that they do so without leaving behind sufficient numbers to produce obvious lesions in these glands has not been established." From experiments on guinea pigs in which a drop of culture of tubercle bacilli placed on the conjunctiva produced a generalised tuberculosis without there being any local lesion Calmette⁽⁹⁾ suggests the possibility of the conjunctiva as a port of entry for the tubercle bacillus in human subjects. In an epidemic of influenza among the troops at Lille in 1918 he found that the percentage of those attacked was very much lower among the soldiers who wore glasses than among the troops in general, and this he thinks adds colour to his views as to ocular infection in tuberculosis. The view which lays greatest importance on direct ærogenous infection of the lungs is the most widely accepted, however, and Cobbett⁽¹²⁾ summarises the evidence for this under three headings:—

- (1) In autopsies on unselected cases lesions are commoner in the bronchial than in the mesenteric or cervical lymphatic glands.
- (2) The rarity of the bovine bacillus in pulmonary tuberculosis.
- (3) Smaller doses are necessary to produce infection by inhalation than by ingestion.

The way in which the tubercle bacillus is inhaled is also still under discussion. The importance of dust and dried sputum is probably exaggerated. Calmette found it difficult to infect guinea pigs by the intratracheal injection of dust contaminated with dried bacilli. On the other hand it was very easy to produce infection by the use of liquid droplets containing the bacilli. The size of the dose is also important. Calmette⁽⁹⁾ has a method by which he can estimate the number of bacilli employed, and for a single dose at least fifty bacilli were found to be necessary to infect a guinea pig. On the other hand a small dose repeated over a period will produce the same effect. Four bacilli every day for ten days readily produced infection. It seems therefore that the danger of infection lies entirely in the droplets of sputum containing the bacilli. The recent experiments of Debré and Coste⁽³⁾ confirming the classical experiments of Flugge, demonstrated this. They exposed guinea pigs in rooms where the examination of pulmonary tuberculosis cases took place and found that the animals were rapidly infected.

THE TUBERCULOUS DIATHESIS.

The question of the tuberculous diathesis is even more controversial than that of infection. This idea would not, however, be gathered from the usual English text books on medicine. Osler discussing the "seed" and the "soil" in tuberculosis deals with the question of predisposition, and quotes the conclusion drawn by Karl Pearson from his statistical studies of the subject that "the diathesis of pulmonary tuberculosis is certainly inherited." Carr in his article in Garrod, Batten and Thursfield's text book on Diseases of Children, writes of the tubercle bacillus that "a diminished resistant power to infection by the microbe may almost certainly be transmitted." Horder, in Price's Text Book of Medicine, states that the existence of the susceptibility to the disease "is one of the cardinal facts of clinical medicine."

There is, however, a considerable body of opinion against these views. Cobbett in England denies that it is proved that a diathesis is inherited, and the modern French school protest strongly against any "inheritance of the soil."

The so-called scrofulous type of child with the *habitus phthisicus* of Hippocrates is probably always already infected. He has the tubercle bacillus shut up in one or more lymphatic gland (Armand-Delille⁽¹⁾). Calmette states that all such children give a positive reaction to Von Pirquet's test. When tuberculosis occurs in children whose parents or even whose grandparents have had the disease, the part played by infection and the alleged part played by some inherited counter-disposition cannot be satisfactorily differentiated from a statistical point of view.

Karl Pearson's⁽¹⁸⁾ work went to prove that the ancestors of tuberculous individuals showed a greater incidence of the disease than the ancestors of the same degree of kinship of normal individuals. Many of his results, however, will support the theory of early familial contagion and the question of

husband and wife infection, subsequently brought in to combat the infection theory, is not relevant since in this connection contagion in early infancy is largely ignored. Drolet⁽¹⁴⁾ quotes the Bang method employed in Denmark of separating new born calves from tuberculous cows: the calves so separated remain free from tuberculosis. Such a method has been of recent years applied to the human subject in France, and its results account for the strong views on the question of predisposition held by many French observers.

Bernard⁽⁶⁾ points out that the very word predisposition is devoid of meaning. The human race is disposed as a whole to tuberculous infection, and if contagion be eliminated offspring of tuberculous parents are no more liable to develop the disease than any other children. His extensive experience has been that if a child be removed at birth from a tuberculous environment it practically never develops tuberculosis. Thus of 2,500 healthy children removed from tuberculous parents by means of the "Œuvre Grancher," only seven cases of tuberculosis occurred. Of 298 infants as distinct from older children dealt with by the Grancher system also removed in this manner, only 11 deaths occurred from all causes. On the other hand Armand-Delille quoted figures at the Rome Congress on Tuberculosis in 1912 which proved that amongst the children of 175 families where open tuberculosis existed 60% of the children became infected and 40% died from the disease. The contrast between these two sets of figures is overwhelmingly against the diathesis theory. Further, Bernard has shown that amongst 127 children born of actively tuberculous mothers the average birth weight was normal, that after birth at least 62% show a perfectly normal growth curve and that congenital defects and deformities are no more common than among the population at large, all points against any inherited diathesis in his opinion. Out of 124 infants who became tuberculous the infection came from the mother in 95, the father in 20, more distant relatives in three and proved contact at hospital in six cases. Out of 108 infants born of mothers suffering from non-contagious varieties of tuberculosis 30 developed the disease, but contagion in these cases could be traced to the father in 20 instances, to other relatives in three, and to other non-related contacts in six, leaving only one child in which contagion could not be proved. Contagion and not diathesis is the cause of the tuberculosis in these infants. Bernard and Debré⁽⁷⁾ consider that there are four main factors which influence the chances of infection in any child:—

- (1) The duration of contact with a source of infection.
- (2) The degree of contact.
- (3) The age at which contamination becomes possible.
- (4) The length of survival of the child after separation from the source of infection.

A prolonged contact of, say, six months for an infant which has been suckled from birth by a tuberculous mother is sufficient to make the chance of infection a certainty. This chance is lessened if the father or other member of the household is the contagious source or if the period of contact is only a

matter of weeks or if the child is over a year old when infection becomes possible.

A consideration of these factors in connection with modern views on immunity to tuberculosis, including the question of "allergy" will explain any case of tuberculosis without any reference to a hypothetical diathesis. Any discussion of the principles involved in the immunity problems, however, is impossible in this brief review of the subject.

ARTIFICIAL PNEUMOTHORAX.

The question of artificial pneumothorax in the treatment of pulmonary tuberculosis in children has practically received no attention in this country. The exhaustive report by Burrell and MacNalty⁽⁸⁾ for the Medical Research Council a few years ago on artificial pneumothorax makes no mention of its application to children nor does Riviere⁽²¹⁾ in his text book on this subject discuss it at all. Both in France and in Germany, on the other hand, this method has obtained a certain amount of popularity. Armand-Delille and others^{(2) (3)} in Paris have employed artificial pneumothorax for a certain number of cases of intra-thoracic tuberculosis. The indications are similar to those in the adult: advancing pulmonary tuberculosis confined to one side, although infection of hilus glands on the opposite side is not considered a contra-indication. Cases of severe hæmoptysis occurring in girls about puberty appear especially amenable to this form of treatment. This author gives a preliminary injection of morphia and employs local anæsthesia. With a Kuss apparatus he injects 25 c. cms. of oxygen at first, after the needle has been introduced in the anterior axillary line in about the fourth space. If the manometric readings show that the needle is in the pleural cavity 250-300 c. cms. of nitrogen are introduced. Refills take place, after an X-ray photograph at 3-4 day intervals for five injections and then every week or fortnight. He observes that children appear to absorb gas quicker than do adults. In the year 1922 out of 230 cases, 22, all with tubercle bacilli in the sputum, were considered suitable for this form of treatment, about 9%. In five of these adhesions prevented collapse. (Even if collapse is incomplete the disease is sometimes arrested.) Of the remaining 17 cases two were allowed to re-expand after 15 months and X-rays showed almost complete absence of any signs of disease. Of the remaining 15, five are in perfect health and the others are all improved. The author points out that to have children with pulmonary tuberculosis alive and well after two years without any cough, with no fever and no tubercle bacilli in the sputum and putting on weight is eminently satisfactory. One case thus treated put on over 20 pounds in the course of a year. In 1923 this treatment was employed for 23 cases out of 262, and of these 16 are "absolutely satisfying." He points out that the course of pulmonary tuberculosis is so rapid in children that most of these cases would have been dead in a few months if pneumothorax treatment had not been instituted. He considers three years necessary to effect a permanent cure.

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In Germany, Eliasberg and Cahn,⁽¹⁵⁾ working in Czerny's clinic, have been employing artificial pneumothorax in children. Out of 659 cases of pulmonary tuberculosis, 125 were considered as suitable, and in 111 the operation was successfully carried out. These workers employ air, as the gas introduced and chloroform anæsthesia is occasionally used for the younger patients.

A large number of these cases were under three years of age, 41 of the series, and among the older children girls at puberty seem particularly apt to suffer from active disease and require treatment. The age distribution is interesting, and is shown in the following graph constructed from the authors' figures for 111 cases—

Age Distribution of Pneumothorax Cases.

They consider that $1\frac{1}{2}$ years is necessary for a cure in cases of hilus tuberculosis, and 2 years as a minimum if bacilli have been found in the sputum, although 3-4 years is probably preferable. Of the 111 cases where the treatment was carried out, 50 had bacilli in the sputum and 61 had not, although clinically were undoubted tuberculosis cases. Of the 50 "open" cases—

13 are living	...	...	...	= 26%
34 are dead	...	...	...	= 68%
3 are untraceable	...	...	...	= 6%

Of the 61 "closed" cases—

45 are living	...	...	...	= 73·8%
9 are dead	...	...	...	= 14·7%
7 are untraceable	...	...	...	= 11·4%

Among the 13 living cases in the first group, one has lived two years, five for three years, five for four years, and two for six years. These results are interesting and are set out in some detail here because there appear to be no other published results of any extended trial of this method of treatment which seems to deserve closer attention in this country.

PROPHYLATIC INOCULATION.

Balfour and Scott⁽⁵⁾ have recently pointed out that the adult mortality rates from tuberculosis are going down and the milk consumption rate is going up, and it is suggested that this may be due to the ingestion of bovine tubercle bacilli in childhood giving rise to some sort of immunity. If then, bovine tuberculosis be eradicated, would we not produce a race of children which would present a virgin soil to infection in later life? But, as these authors point out, the dose of bacilli by this method is always uncertain and undoubtedly for some children is excessive. As Cobbett⁽¹²⁾ has expressed it "the harm done by the bovine bacillus is certain, the benefit it confers is problematical." If ingestion of the bovine bacillus by young children does lead to some sort of immunity, it would appear more scientific to give clean milk and attempt to "vaccinate" children against tuberculosis and produce some degree of immunity at any rate for the first few years of life. Such an imitation of the natural process has long been the aim of the French school and Calmette, Guérin, Weill-Hallé, and others⁽¹⁰⁾ have recently described a special type of tubercle bacillus, which can apparently be used in a living condition without producing any lesions, and which secretes normal tuberculin. This bacillus, known as the "B.C.G." or "Bilié-Calmette-Guérin," has been obtained by culturing the tubercle bacillus for 13 years by means of 230 successive cultures on a 5% glycerine ox-bile potato medium. After all this time the bacillus has become avirulent and can be recultured on ordinary media. The "vaccination" with this bacillus is only effective and must only be employed in cases where there is no possibility of previous infection and its use is therefore confined to the newly-born. Weill-Hallé and Turpin⁽²²⁾ have employed it in over 300 infants since 1922. They use it in cases where the mother is suffering from active tuberculosis and refuses to be separated from her child. Following Calmette's teaching that the predominant route for the natural infection is intestinal, they give the "B.C.G." by the mouth in doses of one c. grm. for three doses on the third, fifth and seventh, or the fourth, sixth and eighth days after birth, half-an-hour before a feed. Of the first 178 cases treated by this method 15 have died, in no case from tuberculosis. This represents a death rate of 8.4%, while the infantile mortality rate in France in 1921 was 11.6%. The remaining cases have been followed up and they remain well and healthy despite the fact that they are submitted to a continuous infection in the home.

A more recent report on the use of the "B.C.G." by Calmette, Guérin and others⁽¹¹⁾ shows that up to June, 1925, altogether 2,070 new born infants had been "vaccinated" in France. Of these cases, scattered in various parts of the country, for many practitioners have applied for the bacillus for their own use, exact details are available in 423, all "vaccinated" at least six months previously. The total deaths from all causes amongst this group amount to 30, a mortality rate of about 7%. Although 137 of these 400 odd cases had been left in contact with some infected person in the family, a tuberculous mother in 86 cases, not one has died from tuberculosis.

Somewhat similar prophylactic measures have been instituted in this country. Pritchard⁽¹⁹⁾ has used injections of various tuberculins for the last 13 years. He usually gives weekly injections to babies for the first six months of life, and he has employed this method in 40 cases, all of which had either a mother or father with active tuberculosis. All these cases are alive and well and the eldest is 12 years of age. Nathan Raw⁽²⁰⁾ found that rabbits could be protected against infection with the bovine bacillus by means of injections of a vaccine prepared from an attenuated human bacillus. He therefore applied a similar method in children who had one or other parent suffering from active pulmonary tuberculosis. He gave two doses at intervals of two weeks of a vaccine prepared from dead cultures of attenuated bovine bacilli. Altogether 412 children, varying in age from 1½ to 14 years have received this treatment. No untoward reaction nor symptom has followed the use of the vaccine, and so far no child has developed tuberculosis, although as this author points out some time must elapse before the value of this method can be judged. At any rate these three methods of "vaccination" against tuberculosis here described seem to point to a scientific imitation of what some believe to be a natural immunity process which is said to occur in a large percentage of the population and as such deserves extended trial.

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