Professor Norman B. Capon and Professor Stanley Graham respectively.

I wish to express my gratitude to all who have been associated with this work, especially the medical staffs of these hospitals.

REFERENCES

- Blacklock, J. W. S. (1932). *Spec. Rep. Ser. med. Res. Coun.*, No. 172. London.
 Caffey, J. (1945). *Pediatric X-ray Diagnosis*. Year Book Publishers, Chicago.
 Medical Research Council (1948). *Lancet*, 2, 862.
 Naish, A. E. (1933). In *Diseases of Infancy and Childhood*, edited by L. G. Parsons and S. Barling. London.
 Nelson, W. E. (1946). In *Mitchell-Nelson's Textbook of Pediatrics*, 4th ed. Saunders, Philadelphia.

SOME PRACTICAL PROBLEMS OF TUBERCULOSIS IN CHILDHOOD*

BY

F. M. B. ALLEN, M.D., F.R.C.P.

Nuffield Professor of Child Health, Queen's University, Belfast

It is strange to learn that while Aristotle realized that tuberculosis was an infectious disease Laennec believed it was not contagious, and Koch held that bovine tuberculosis could not be communicated to man. Now it is generally accepted that the majority of infants and children, particularly those living in urban civilized communities, are infected early and develop a high degree of immunity; otherwise few would survive under the housing conditions we have inherited from the industrial revolution of the nineteenth century. It has been long recognized that good ventilation, general cleanliness, and the proper disposal of sputum diminish the risk of repeated massive doses of infection and reduce the incidence of primary infection and reinfection. A health commission sitting in Florence in 1754 reported that "phthisical patients who lived in large airy rooms did not require more than that their rooms should be well cleaned and always purified by widely opened windows; but that stuffy rooms with still air increased the danger to others" (Burrell, 1933).

Susceptibility of Infants

The infant and child are more susceptible than adults, and the younger the patient the greater the risk. Newsholme (1926) says one of the most important problems is how to minimize the risks of infection in the first five years, and especially in the first two years. Kayne (1935) points out that both infection and mortality are greater where the contact is with a parent than with a more distant relative; and with the mother more than with the father. This is obviously explained by the more frequent and intimate association with the mother than with any other member of the household, an exception being the tragic event in which a healthy mother leaves the care of her infant mainly to a "nannie" or nurse who unknowingly is infective. The infant lives strictly within the family, whereas older children share their time at school, out-of-doors, and at home; so that if a parent become infectious he or she may or may not infect the older children, but the toddlers are more likely to be infected, and the infant almost certainly will be.

Infection is known to occur at all ages. My youngest case was diagnosed at 8 weeks (and died three days later), another case at 3 months, and recently one at 7 months. Lemaire (1925) found that if contagion arose before 1 year the mortality was 57%, if between 1 and 2½ years it was 1.66%. Nassau and Zweig (1925) found that of twenty

*Address given to the Nottingham Medico-Chirurgical Society on Nov. 17, 1948.

infants infected during the first three months all died; of sixteen infected during the second three months 18.75% died, and of thirteen infected between six and twelve months 3.8% died. Asserson (1927) states that of those infected under 12 months 15% died, and of those between 1 and 2 years 2.6% died. These figures show in general that tuberculosis in young infants carries a heavy mortality, but the chances of survival increase rapidly thereafter.

Mode of Infection

It is now generally accepted that the majority of cases of childhood tuberculosis are the result of human contact. It is certain that almost every case of intrathoracic tuberculosis is of the human type, and all but a few of the cases of abdominal, bone, and joint disease are of bovine origin.

Human Contacts

Infection of infants and children may arise as a consequence of the intimacy of the home environment. In the case of the child diagnosed at 8 weeks the post-mortem examination showed the condition to have been tuberculosis with extensive caseation of the tracheo-bronchial glands. The contact was proved to be the grandmother, who had come into the household to assist her daughter during her confinement by undertaking her household duties and "looking after" the newborn infant. The grandmother was found to have fibroid phthisis with a positive sputum. You will in this connexion remember that Madame Curie (1938) never understood as a child why her mother would never kiss her; she realized afterwards that her mother was consumptive and later appreciated to the full the loving restraint exercised.

Blacklock (1947), in a series of 144 cases of tuberculous meningitis, showed that the source of infection was most often the mother: mother 44%, father 22%, sister 21%, brother 20%, aunt 12%, uncle 6%, grandmother 2%, grandfather 6%, others 11%. What is true of tuberculous meningitis applies to other forms. It is inadequately realized that tuberculous meningitis arises just as effectively from a focus in the chest as from one in the abdomen, and, as there is much more intrathoracic tuberculous infection than abdominal, the majority of cases of tuberculous meningitis are found to be of human origin. McMurray (1944) showed in my series of 24 cases that 72% were human type organisms.

The explanation of the tuberculous mother's complicity is that the infant is exposed by its close contact during nursing, fondling, dressing, etc., to the risk of inhaling a massive dose of bacilli and to repeated infections. Where the mother's position is superseded or supplanted by a grandmother, an aunt, or a domestic who is infectious, the risk is obviously an equal one. In the case of older infants and young children it should be remembered that school-teachers—not forgetting nursery-school and kindergarten teachers—who are the victims of the disease may infect their pupils. The Report of the Children's Committee of the Joint Tuberculosis Council (1948) gives the example of a sputum-positive schoolmaster in whose class two children died of tuberculous meningitis and 45% of the children were found to be tuberculin-positive: in another instance a teacher with positive sputum was probably responsible for two deaths from meningitis. I have a number of records where the domestic servant (and in one case a children's nurse) was entirely unsuspected of having phthisis until tuberculosis was diagnosed in a child in the family and the unsuspected disease discovered.

Indirect infection of children from the inhalation of dust containing dried tuberculous sputum, due to the careless disposal of this highly infectious material, is difficult to prove. But it behoves the infected adult to be considerate of others,

especially the young of the community, and to adopt the highest principles of hygiene in this respect. The tuberculous public must be properly educated in the risk of contagion which they carry and the means by which the risk can be diminished.

Milk-borne Infection

Practically all abdominal tuberculosis is the result of bovine infection due to the ingestion of infected milk. It is possible, though probably rare, for dust contaminated by dried human tubercle bacilli to cause the disease, just as in some instances the inhalation of bovine bacilli from an infected cow can account for pulmonary infection.

A large proportion of cows in this country are tuberculous, probably 40%. Fortunately not all of these excrete tubercle bacilli in their milk, though they give a positive tuberculin reaction. Less than 1% suffer from tuberculosis of the udder, and it is these animals which are almost wholly responsible for unsafe milk. It should be realized that cows suffer from pulmonary tuberculosis; they cough like humans, and disseminate tubercle bacilli in the byre, exposing their bovine colleagues (and byre-workers) to the risk of infection. They (again like humans) swallow their sputum and almost certainly excrete tubercle bacilli in their faeces. In an unhygienic byre, therefore, it is easy to understand how a cow's udder may become contaminated with infected excreta, and through the absence of simple hygienic precautions the milk becomes a menace to those who consume it in a raw state.

This unsatisfactory situation can be overcome by securing a larger and larger proportion of non-tuberculous cows. In the U.S.A. only 0.5% of cows are tuberculous, in Canada 2%, and in New Zealand 4.5%; whereas in Switzerland, the Netherlands, Denmark, Belgium, France, and Britain the figures vary from 20 to 40% (Lord Bledisloe, 1948). In Denmark the incidence is now reported as being less than 10%. Encouragement should therefore be given to the agricultural industry to produce tubercle-free milk, and there is no doubt that this is the best solution from a health point of view as well as for economic reasons.

Effective pasteurization or home sterilization of the milk will render it safe for human consumption. Commercial pasteurization, however, entails elaborate plant which must be subject to frequent inspection and testing for efficiency and thus adds to the basic cost of production. In addition, it puts a premium on dirty milk and will never encourage the widespread production of tubercle-free milk from non-tuberculous cows. The problem of the supply of raw milk which is safe will require the education of milk producers and their conversion to this practice, the provision of adequate incentives, and better conditions for milk-producing cattle than exist on many farms to-day.

It should be widely known that the use of raw milk which does not come from a tubercle-free herd is a grave risk to infants and young children. It is a tragic indictment of present-day conditions to see a child suffering from widespread abdominal tuberculosis as a result of a holiday or a brief visit to a relation in the country, where it has unfortunately consumed infected milk, the parents having always provided safe milk at its home. We should regard tubercle-infected milk as a gross example of food-poisoning, and we as a profession should appeal continuously for the universal provision of milk which is safe, preferably because its source is beyond reproach or, failing this, because it has been effectively pasteurized. Until this has been achieved all other milk should be boiled, just as are eggs and potatoes.

The Tuberculous Lesion

The histology of the tuberculous lesion is characteristic, consisting at first of a focus of large mononuclear cells

containing tubercle bacilli which may subsequently proceed to caseation, liquefaction, fibrosis, or calcification.

The primary lesion is the result of an invasion of a tissue or organ by tubercle bacilli, and the illness of the primary pathology is known as the primary tuberculous complex. Parrot (1876) gave the original description of the lung lesion, and Ghon (1912) recorded his observations of detailed search of the lungs in the post-mortem room for the primary focus. Along with Cohnheim and Ranke, Ghon was responsible for controverting Calmette's view that intrathoracic tuberculosis was the result of lymphatic spread from the mesenteric glands. Ghon's primary lung focus is now accepted as the initial pathological lesion of intrathoracic infection. This is followed by a tuberculous lymphangitis spreading from the focus to the lymph glands draining that area, and finally by changes in these glands of an inflammatory and usually caseous nature. This triad of changes is known as the "primary lung complex." It will be appreciated that this is a centripetal spread (characteristic of tuberculosis in childhood), as distinct from the centrifugal spread of the adult lesion. Also the childhood lesion is notoriously difficult to detect by clinical means alone, as it is rarely, even with involvement of the lymph glands, large enough to produce physical signs.

Should the pathological process undergo arrest the only clinical change noted is that after an interval, which may be up to six weeks, the child now reacts to the intradermal injection of diluted tuberculin and becomes Mantoux-positive. The tuberculin test is a fine screen available for the diagnosis of the first infection with tuberculosis in childhood. "It detects the presence of the disease long before other methods of examination are of any avail, and in the majority of cases remains the sole diagnostic agent during life" (Myers and Harrington, 1934).

The primary lesion, having undergone arrest, may be discovered as a result of radiological examination in a number of cases. Its presence should, however, be suspected by the discovery of associated phenomena—an area of pulmonary collapse, or obstructive emphysema due to complete or incomplete blocking of a bronchus; pulmonary collapse may be quite extensive and confounding on clinical examination. Pleurisy, erythema nodosum, and phlyctenular conjunctivitis are other manifestations associated with the primary tuberculous complex. Epituberculosis is sometimes regarded as being associated with the primary lesion. This term was introduced by Eliasberg and Neuland (1920), and is probably "a benign pneumonic consolidation not histologically tuberculous, but conditioned by a state of tuberculin allergy."

Wallgren and Lundblom (1935) estimated that a period of from five to six weeks elapsed between the primary infection and the development of erythema nodosum, from three to six months before pleurisy would arise, up to three months before the onset of tuberculous meningitis, and less than three years before the involvement of bone and joint structures.

Post-primary Tuberculosis

Tuberculosis may eventually involve any structure or organ in the human body. It is estimated that a period of three months is required to ensure healing of the primary focus, and upwards of two years may be necessary for complete arrest of the pathological process in the affected glands. If the process is not arrested in the primary stage the subsequent lesions are regarded as "post-primary." There may be a haematogenous dissemination to other organs resulting in miliary tuberculosis with or without meningitis, caseous tuberculosis of organs such as spleen, liver, kidneys, etc., or the primary complex may disintegrate, giving rise to the "bronchogenic spread."

Symptoms and Diagnosis

The primary infection may be relatively symptomless. It may be indicated by an ephemeral malaise, and be quite excusably regarded as a chill or the result of over-indulgence of appetite or an indiscretion in diet, and receive the routine homely remedy of purgation. Sometimes pyrexia is marked at the onset and may persist at a lower grade for some days, and the child may be subjected to routine investigation which will reveal radiological evidence of a primary lung lesion, or one of the features of the primary complex or associated phenomena, pleurisy or enlarged tracheo-bronchial glands, and a positive Mantoux reaction. Recently I saw an infant of 7 months suffering from an apparent attack of asthma. The tuberculin test was positive, x-ray examination of the chest showed an obstructive collapse of the right upper and middle lobes, and tubercle bacilli were recovered from stomach washings after some weeks. It has since died (vide Barsby, 1941).

It is true, therefore, that the primary lesion and often the immediate succeeding changes are unsuspected. An unexplained temperature should always raise a suspicion, however, and precipitate investigations, which will include skin testing, an x-ray examination, and estimation of the sedimentation rate.

It is not my intention to proceed further with either the symptoms or the diagnosis, because consideration of these would involve a review of the symptomatology of the well-recognized manifestations of tuberculosis, prolonged descriptions of which are adequately recounted in standard textbooks.

I would like to emphasize that a negative radiological examination does not in all cases exclude the presence of a primary infection. Myers and Harrington (1934) state that x-ray examination fails to locate the lesion of first-infection type in 75% or more of children who react to the tuberculin test; and usually in the 25% in which a lesion is located no clinical significance is attached to it. Likewise when the routine 1 in 1,000 Mantoux is negative the test should be repeated with the stronger dilution if the disease is to be finally excluded. In more than one instance a strongly positive reaction has occurred to the 1 in 100 dilution test done ten or more days after the weaker one, and I sometimes wonder if the first test was not made before the sensitization process was complete.

If a primary lung focus has been discovered the question arises whether or not post-primary extension of the disease is responsible for the illness. I can only emphasize the importance in diagnosis of an adequate history of the illness and a complete physical examination of the patient, with an assessment of the clinical picture in the light of professional experience and mature judgment.

Prevention and Treatment

The prevention of this disease and its eventual eradication depend on many factors, and a successful campaign must therefore be a comprehensive one. It must include the education of parents and those in charge of children in the fundamentals of tuberculosis and its incidence, of doctors in the recognition of the life history and pathology of the disease, and of social workers, students of economics, and the whole agricultural community in the relationship between their various interests and the problem of the prevention of this scourge. Public health services must be stepped up and contacts sought for, nutritional standards maintained or raised, housing improved, and hospital accommodation and facilities provided for the isolation and care of infective patients and contacts, as well as for those who are victims of a primary lesion, so that adequate rest may

be attained. B.C.G. vaccination must be considered. Streptomycin is under trial, both for the established case and for the primary infection, and perhaps other remedies are in process of discovery.

Tuberculosis thrives and flourishes on ignorance—ignorance of its cause, of its spread, and of means of its prevention. McNeil (1929) said that "education of the people in the fundamental facts is still needed and ought to keep an important place in medical preventive measures. There is still need not merely for preaching the truth but also for denouncing error. The old heresy that tuberculosis is a hereditary disease, fatally transmitted from parents to children, still lingers in the minds of many and blinds them to the real dangers. It should be possible for all to know and understand the simple essential facts of tuberculous disease in children and of its transmission by milk and man."

If all the milk supplied in this country was safe bovine tuberculosis would disappear, as it has largely done in Canada and U.S.A. The discovery of contacts and their proper care and treatment should be the responsibility of an enlightened public health service, so that these patients could be given the appropriate treatment in the early stages and, for preference, be isolated until they were no longer a menace to those who share their environment. Doctors must exercise constant vigilance and use all the available resources to secure an early and accurate diagnosis—in the child by suspecting the disease in the face of indeterminate signs and symptoms, in the adolescent and adult on evidence of a departure from good health. Mass radiography undoubtedly detects a number of cases which would otherwise be lost; but it is not accepted as an adequate means by which the disease can always be excluded. Reinfection or reactivation must always be borne in mind.

The development of a new infection on a tissue already sensitized provokes a specific reaction which is readily detected by radiological examination. I do not propose to travel far in the field of social economics except to emphasize that good housing and economic security are favourable factors. Crowded living conditions associated with bad ventilation are conducive to the spread of the disease; an inadequate family income usually means sacrifice of the nutritional needs because the "standing charges" of rent, taxes, light, and perhaps heat have all of necessity to be met. There is no useful purpose in settling families in a "garden village" of better homes at an increased rent, additional costs for travelling, etc., unless the family budget can meet these costs without sacrificing the nutritional needs.

B.C.G. Vaccination

B.C.G. vaccination has not been tried in this country as yet. In Canada and on the Continent it is used with enthusiasm in immunizing tuberculin-negative infants and children, particularly those who have to live in tuberculous households. Wallgren has been using B.C.G. in Sweden since 1926, and maintains that vaccinated children are protected against the disease for a period of from two to ten years, during which time they will probably have acquired subclinical tuberculosis and therefore remain relatively immune. Experience in Sweden is impressive; B.C.G. vaccination scars in children are as common as smallpox vaccination scars in this country. One cannot but be attentive to the statement of Malmros (1948): "When a case is admitted to any hospital with the diagnosis of tuberculosis or suspected tuberculosis it is ascertained whether the patient has been vaccinated with B.C.G. By this means it is possible to find out whether any of those vaccinated have developed tuberculosis. During the period 1942-7

only one such case has been discovered." It appears that in this case vaccination has not given enough resistance because of deficient power of reaction. Frappier, of Montreal, hopes in the course of the next few years to have every child in the province of Quebec vaccinated with B.C.G. vaccine.

B.C.G. vaccination has been criticized and subjected to condemnation largely as a result of unfortunate experiences which can be eliminated by the observance of better technique in the preparation of the vaccine and its administration. Complications of the inoculation undoubtedly arise, but they can be avoided by proper precautions. Wilson (1947) has been critical of the suggestion that the practice should be adopted in this country, and has been replied to by Wallgren (1948). It would seem only fair that a scientific investigation of its efficiency in this country should be carried out with proper controls before embarking upon a national venture which by its biological nature will be damned outright by a section of the community.

Streptomycin

Streptomycin seems to have some control over the progress of tuberculosis in that the original experiments on guinea-pigs proved that the drug would arrest and even partially eradicate well-established tuberculosis in that animal. Hinshaw and Feldman (1945) recorded a favourable response in two-thirds of 75 cases, in some a clinical cure being recorded. Apart from a few unpleasant reactions depending upon dosage, impurities in the preparation, and idiosyncrasy, there is the disadvantage (and it is a disquieting one) that some types of tubercle bacilli are resistant to streptomycin. It would appear that these resistant strains, freed from the dominant restraint of the previously active ones, may infect other individuals and multiply in spite of streptomycin administration and account for much of the deterioration of cases under treatment after the initial improvement (M.R.C., 1948). There is the further consideration that a resistant strain can initiate the disease in other individuals and account for the widespread dissemination of the disease in a form for which streptomycin is innocuous.

In miliary tuberculosis a favourable response is obtained in a number of cases, but post-mortem examinations of fatal cases of tuberculous meningitis do not provide any histological evidence that the tuberculoma has been influenced by the drug; the associated meningeal exudate, however, may show considerable organization and thus account for the clinical improvement. There is a suggestion of a field of usefulness for streptomycin in primary infections, but it will be necessary to review the evidence when an extended trial has been made and a critical review is possible.

Conclusion

I have now completed my task within the limits of time and my competence. I shall not have failed, however, if I have focused attention upon some of the practical aspects of a common disease in infants and children, a disease which carries a heavy responsibility for death, sickness, and incapacity. If I began at the beginning it was because, as Aristotle said, "He who sees things from their beginning will have the finest view of them." If we study and understand tuberculosis in all its aspects in the young we will appreciate all the better the disease in the adult; so that nothing is lost, but perhaps much may be gained, by this approach. By concentrated effort in the preventive field and the use of all available facilities for diagnosis and treatment we can look forward with more hope for its eventual eradication.

REFERENCES

- Asserson, M. A. (1927). *Amer. Rev. Tuberc.*, **16**, 359.
 Barsby, B. (1941). *Lancet*, **1**, 627.
 Blacklock, J. W. S. (1947). *British Medical Journal*, **1**, 708.
 Bledisloe, Lord (1948). *The Times*, Oct. 30, p. 5.
 Burrell, L. S. T. (1933). *Med. Pr.*, **187**, 20.
 Curie, Eve (1938). *Madame Curie*. Heinemann, London.
 Eliasberg, H., and Neuland, W. (1920). *Jhrb. Kinderheilk.*, **93**, 88.
 Ghon, A. (1912). *Der primäre Lungenherd bei der Tuberkulose der Kinder*. Berlin.
 Hinshaw, H. C., and Feldman, W. H. (1945). *Proc. Mayo Clin.*, **20**, 313.
 Joint Tuberculosis Council (1948). Report of Children's Committee.
 Kaye, G. G. (1935). *British Medical Journal*, **1**, 694.
 Lemaire, H. (1925). *Rev. Tuberc.*, **6**, 228.
 McMurray, J. (1944). *Arch. Dis. Childh.*, **19**, 87.
 McNeil, C. (1929). *British Medical Journal*, **2**, 657.
 Malmros, H. (1948). *Ibid.*, **1**, 1129.
 Medical Research Council (1948). *Ibid.*, **2**, 769.
 Myers, J. A., and Harrington, F. E. (1934). *J. Amer. med. Ass.*, **103**, 1534.
 Nassau, E., and Zweig, H. (1925). *Z. Kinderheilk.*, **39**, 484.
 Newsholme, A. (1926). *Lancet*, **1**, 1022.
 Parrot (1876). *C. R. Soc. Biol., Paris*, **28**, 308.
 Wallgren, A. (1948). *British Medical Journal*, **1**, 1126.
 — and Lundblom, A. (1935). *Nord. med. Tidskr.*, **10**, 1699.
 Wilson, G. S. (1947). *British Medical Journal*, **2**, 855.

THE EFFECT OF ENDOCRINES ON FIBRO-ADENOSIS

BY

H. J. B. ATKINS, D.M., M.Ch., F.R.C.S.

Director of the Department of Surgery, Guy's Hospital

A clinic for the investigation and treatment of the painful nodular breast was established at Guy's Hospital in 1937, and except during the years 1941–5 it has been functioning weekly since that date. At different times I have been assisted in the running of the clinic by various workers, but my thanks are due particularly to Dr. P. M. F. Bishop, endocrinologist to the hospital, who launched the project with me, and whose advice has always been available. All expenses incurred in the investigations have been defrayed by an annual grant from the British Empire Cancer Campaign.

I originally set out to investigate the effect of endocrine preparations on the disease which we now call fibro-adenosis, defined as "a painful or nodular condition of the breast not due to new growth, bacterial inflammation, or fat necrosis" (Atkins, 1938). As this part of the investigation is complete I am submitting a report of the findings. The clinic is at present devoted to a clinico-pathological investigation into the effect of endocrines on established cancer of the breast and to following up the now considerable series of cases of fibro-adenosis.

A report has already been given of the early work in connexion with the administration of oestrogens, and androgens in the form of injections of testosterone propionate (Atkins, 1940), but a brief recapitulation of our findings may not be out of place.

Bearing in mind the importance of the psychological aspect of this condition and the subjective nature of many of the manifestations, together with the absence of any absolute standards of such objective phenomena as "nodularity," we were careful to control our results by submitting a parallel series of cases to a course of injections of sterile olive oil if the subsequent therapeutic agent to be investigated was to be injected, and to a course of chalk pills if the agent was to be taken by mouth.

In nearly every case a random sample of breast tissue was taken by biopsy from that part of the breast where the disease was judged to be most advanced, and submitted to histological examination. A second sample was taken at the conclusion of the treatment and at a corresponding