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FAMILY TUBERCULOSIS DUE TO BOVINE TUBERCLE BACILLI

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Although by the end of 1933 nearly eighty cases of bovine phthisis pulmonalis had been discovered in Great Britain no evidence had been obtained of transmission of the bovine bacilli from one human being to another. It was, indeed, seldom possible to elicit a history of clinical tuberculosis in another member of the household in which a bovine case had occurred.

In 1934 Walker¹ reviewed the recorded instances where in a household containing one case of bovine phthisis one or more of the other members of the family suffered from tuberculosis, and reported in detail the bacteriological findings in two families each with two cases of pulmonary tuberculosis. In one family a girl of 20 was found (at Glenlondond Sanatorium) to be expectorating bovine tubercle bacilli with the sputum. Her mother also suffered from pulmonary tuberculosis, and her sputum, which was examined bacteriologically at Cambridge and Glenlondond, yielded cultures of the human type. In the second family there were two brothers, both of whom suffered from phthisis pulmonalis. Dr. W. M. Cumming, having shown that one brother, a man aged 48, was discharging bovine tubercle bacilli with the sputum, examined the sputum of the other, a man of 60. The sputum of the latter yielded typical eugonic human cultures. In four other instances two or more members of a family containing a case of bovine phthisis suffered from tuberculosis, but in none of these cases was material from the other members available for examination.

Thus bacteriological evidence was lacking of the occurrence in a household of a case of bovine tuberculosis in association with a case of bovine phthisis. We do not mean to imply that bovine infection has never been demonstrated in more than one member of the same family. One of us (A. S. G.) has reported the four following instances of such occurrence, but in all of these the cases of tuberculosis were non-pulmonary.

In one family twin boys both developed lupus vulgaris at the age of 3 years. When they were 10 years old lupous tissue was excised for bacteriological investigation, and bovine tubercle bacilli were cultivated from the lesions in each case. The boys were breast-fed, and were afterwards given cows' milk unboiled. The parents were healthy, and there is little doubt that in this instance the source of the bovine bacilli was the cows' milk.

In the second family a brother, aged 10, and a sister, aged 16, both had lupus, which in the boy was limited to the chest and in the girl was generalized and associated with scrofuloderma and tuberculosis of the spine, elbows, and fingers. From each child bovine bacilli were cultivated, which in the case of the boy were fully virulent and in that of the girl were definitely attenuated, though in cultural characteristics they were identical.

In the third family there were two sisters, aged 16 and 8 years respectively, with glandular abscesses in the neck,

which the elder girl, who also showed keloid scars from old lupus, had had for seven years and the younger for thirteen months. Fully virulent bovine tubercle bacilli were cultivated in each case from abscess pus, the interval between the two investigations being ten months. These children were evidently infected at different times, and it is possible that the younger child might have been infected by the older.

In the fourth family there were three sisters, aged 8, 15, and 17 years, who had suffered from tuberculosis for seven, five, and eight years respectively. Each girl had multiple scrofulodermic abscesses (neck or arms) and a thickened, scaly lupoid condition of the hands or fingers. In addition, the youngest girl suffered from peritoneal tuberculosis; the second girl had had an excision of cervical glands two years previously, and the third had had some knee-bone tuberculosis, which was cured. Bovine tubercle bacilli were obtained in culture from each girl, four strains from the youngest (two scrofulodermic abscesses, lupoid skin, and a peritoneal nodule) and one each from scrofulodermic abscesses in the two older girls. The strains from the two older girls and those from the skin and peritoneum of the youngest were attenuated, while the two abscess strains of the last were fully virulent.

We are now, as a result of the investigations of 1934, able to give details of two families, each of which contained two cases of phthisis pulmonalis in adults and one, in addition, a case of glandular tuberculosis in a child, all due to tubercle bacilli of the bovine type.

Family A

In April, 1934, when discussing together the absence of proof of transmission of bovine tubercle bacilli by human beings, Dr. C. C. Finlator, medical officer of health for the county of Clackmannan, informed us that he had under his care a brother and sister with phthisis pulmonalis whose mother had been a milker and was afterwards notified as a case of pulmonary tuberculosis. We agreed that a bacteriological examination of these cases should be made, and Dr. Finlator, to whom we are also indebted for the clinical particulars of the cases, kindly undertook to collect specimens of sputum and to forward them to Cambridge for investigation. Specimens were obtained from the brother and the sister, and both, to our surprise, were found to contain tubercle bacilli of the bovine type only. Unfortunately, no material was available from the mother, who at this time was well, without cough or sputum, and had been doing work on a farm for some years. She was born in February, 1887, and married in 1903. She had ten children, the first in 1904, the last in 1924, and was notified as a case of tuberculosis in June, 1916, a month after the birth of her seventh child. Her illness began with cough and loss of strength and weight; she also had slight breathlessness and night

sweats. On examination both upper lobes were found to be involved. She was treated at home, where she occupied a separate room, and gradually improved, though for some time there was considerable sputum. The sputum was examined microscopically several times during Dr. Finlator's absence on war service, when the illness occurred, but tubercle bacilli were not found. Of the ten children one died in early infancy from general weakness; six are healthy; one, a girl aged 13, in 1932 had pleurisy with effusion at the right base and a small patch of infiltration at the right apex, which cleared up in 1933, and she is now well and working. The two remaining children—the brother and sister previously mentioned—developed pulmonary tuberculosis, and were the subjects of bacteriological investigation. There was no history of tuberculosis in the father, who died in 1927 from shock following a bicycle accident.

The son was born in July, 1905, and was healthy until he attained the age of 26½ years, when he had an illness which began with pain in the right side, followed by cough and progressive loss of weight. Three months later (February, 1931) he was notified as a case of pulmonary tuberculosis. Examination then showed defective expansion of both sides of the chest, slight dullness and coarse friction at the right base, and a few fine crepitations, with some bronchial breathing in the left upper lobe just below the clavicle; there was no sign of cavity formation. He did well in the local tuberculosis hospital during his stay from February 26th to July 3rd, 1931; physical signs and symptoms subsided, and he gained 25½ lb. in weight. From the hospital he was transferred to a sanatorium, where he stayed two months, leaving of his own accord. He had then very little sputum, containing a few tubercle bacilli. The lungs were dry, but there was slightly increased vocal resonance over the right upper lobe and some bronchial breathing over both upper lobes. He returned to farm work, and Dr. Finlator did not see him again until March, 1934, when he had a relapse, the condition of the lung, especially on the right side, being very similar to that in his first acute phase. He was admitted to the local hospital in March, 1934, and was discharged in September, 1934, fit for light work. The physical signs had subsided again, and his general condition was fairly good. Sputum was scanty, but still positive. In January, 1935, his condition was fairly good, and nutrition and capacity for exercise were better than they had been for some time. Moist sounds in the lungs were few, but the sputum still contained tubercle bacilli. He was particularly fond of milk, but has had no glandular swellings in the neck. He is not married.

BACTERIOLOGICAL INVESTIGATION

Specimens of sputum were received at Cambridge on May 17th and July 6th, 1934, and January 19th, 1935. Microscopically tubercle bacilli were scanty in the first, fairly numerous in the second, and not found in the third specimen; the bacilli were short and rather plump. Cultures of tubercle bacilli were obtained directly from each specimen, the colonies being in moderate number from the first, numerous from the second, and sparse from the third. The primary colonies and the subcultures of each strain were typically bovine. The first strain was inoculated subcutaneously (dose rather less than 4 mg.), the second and third intravenously (doses 0.01 mg.), each into one rabbit. The rabbits died of typical general miliary tuberculosis in forty-one, thirty-one, and twenty-six days respectively.

The daughter was born in May, 1907, and after leaving school worked in a paper-mill until she married at the age of 18. She had never milked cows, was not particularly fond of milk, and had not had enlarged neck glands. There were five children—one girl and four boys—the ages of whom (in 1934) ranged from 10 to 2½ years. They have been recently (in 1935) examined by Dr. Finlator,

who reports that they are all in excellent health. The husband, aged 31, is a well-nourished man of good physique. He also has been examined by Dr. Finlator and shows no physical signs of tuberculosis in the lungs, abdomen, or glands, and has no sputum. The woman was quite healthy up to November, 1933, when she started a cough, which persisted. By February she had begun to lose weight and to perspire freely at night. Sputum was copious. She became progressively worse, and was admitted to hospital in May, 1934, in a grave condition. On admission there was clinical evidence of cavity formation at the right apex, and after a few weeks in hospital signs of gross cavity formation became evident on the left side also. The sputum was all the time very copious and purulent. She had attacks of diarrhoea at the onset of her illness and also in hospital, where she died in July, 1934.

NECROPSY

This was made by Dr. M. S. Stevenson, medical superintendent, Clackmannanshire Combination Infectious Diseases Hospital, to whom we are much indebted for specimens and notes of the post-mortem findings. The parietal and visceral pleurae were largely adherent. Most of the left lung from the apex downwards was completely destroyed and converted into a sac filled with purulent fluid; the lower part of this lung was infiltrated and so friable that it came away in shreds when an attempt was made to remove it. The upper lobe of the right lung was also destroyed and converted into a bag of pus; the lower lobe, of which portions were sent to Cambridge, showed caseating pneumonic patches (t.b.++), containing small cavities; another portion was crepitant. The right tracheo-bronchial glands (sent to Cambridge) were very anthracotic, not obviously enlarged, and without caseation or calcification. The left tracheo-bronchial glands were not distinguishable at the necropsy, owing to the complete destruction of the left lung.

The mesenteric glands (sent to Cambridge) contained three completely calcified nodules—the largest 10 mm., the smallest 2 to 3 mm., in diameter. The stomach and intestines showed no abnormality. Liver and spleen slightly enlarged, no tubercles seen. Heart small and anaemic; pericardium filled with serous fluid.

BACTERIOLOGICAL INVESTIGATION

Specimens of muco-purulent sputum (t.b.++) were received on May 17th and June 23rd, 1934. The bacilli were mostly short, some uniformly stained, some beaded. Pure cultures of bovine tubercle bacilli were obtained directly from each specimen. Cultures of tubercle bacilli identical with the sputum strains were also obtained directly from the lung and through the guinea-pig from the right tracheo-bronchial gland of the woman. (No tubercle bacilli were demonstrated in a calcareous nodule from a mesenteric gland, an emulsion of which did not produce tuberculosis in a guinea-pig.) The virulence of each of the four strains of culture was tested on the rabbit, the first strain by subcutaneous inoculation (dose 2 mg.), the other three by intravenous inoculation (doses 0.01 mg.). The four rabbits died of general tuberculosis in seventy-one, thirteen, twenty-two, and thirty-one days respectively.

Family B

In this family three persons—a man, his wife, and a child—were examined bacteriologically. The woman was the first to come under our observation—in July, 1933—when she was admitted to Glenlond Sanatorium. On admission she was very ill, with severe cough, abundant sputum, and considerable systemic disturbance. She was thin—weight only 5 st. 7½ lb.—very pale, and somewhat dyspnoeic. Examination of the chest revealed extensive disease of both lungs, with more moist sounds on the left than on the right side. Chains of shotty glands were palpable in the posterior triangles of the neck. The larynx was involved, but there were no signs or symptoms of intestinal disease, and no tubercle bacilli were found in the urine. The sputum was laden with tubercle bacilli, which, for the most part, were long, curved, and beaded. It

was therefore remarkable to find that the bacilli in culture had the characters of dysgonic bovine tubercle bacilli, and, furthermore, fell below the standard of bovine viruses in virulence. The patient improved with rest, and left at her own request in June, 1934, with little change in the physical state, but with less systemic disturbance.

When it was established that the bacilli present in the sputum of the woman were identical culturally with bovine bacilli the importance was seen of examining the other members of the family, some of whom were known to be tuberculous.

The husband, who was then living in Fifeshire, sent specimens of his sputum to Glenlomond and to Cambridge for examination. The sputum contained numerous tubercle bacilli, which, as in the first case, were mainly long and beaded. Cultures of the bacilli were obtained, and, most surprisingly, proved to be dysgonic and identical with the wife's strain, alike in cultural characters and in having lower virulence than standard bovine strains.

The children, of whom there were three, were then examined clinically, having been admitted to Glenlomond Sanatorium for the purpose. They all reacted to the intradermal tuberculin test. A gastric lavage was done in each case and the deposits were inoculated into guinea-pigs. A positive result was obtained in one case and a culture from the tuberculous lesions of the guinea-pig proved dysgonic and highly virulent for the rabbit.

The question then arose as to the relation of the three strains of bacilli one to the others, and in order to elucidate this point it was necessary to go very thoroughly into the personal and family histories of the parents. We are much indebted to Dr. W. A. Muir, medical officer of health, Gillingham, Kent, for verifying and amplifying the details of history given to us by the wife (Mrs. T.).

She was born in 1904, in a rural part of Kent, and was breast-fed for about nine months and then afterwards was fed on cows' milk, which was not always boiled. At the age of 4 she had measles, followed by bronchitis and pleurisy, with effusion, and thereafter she was always "bronchial." She attended school, however, fairly regularly, and had only one long absence, at about the age of 10, when she was in bed for a month with fever and cough and was a month in convalescence. When aged 16 or 17 she was anaemic and had a cough, and, according to her statement, which could not be verified, visited the tuberculosis dispensary regularly with a sister, but apparently no definite diagnosis of tuberculosis was made, or, at least, the case was not notified. She married in 1923, at the age of 18, and has three children, aged 10, 8, and 6, the youngest born in 1927. After the birth of the third child she never felt well, and in 1929 was diagnosed as suffering from pulmonary tuberculosis. In 1930 she was admitted to a sanatorium in Kent, but left of her own accord. The sister, previously mentioned, now 26 years of age, was notified as suffering from pulmonary tuberculosis in October, 1922. Her illness followed influenza with chest complications in 1918. According to the local tuberculosis register her disease was quiescent in 1925 and cured in 1927. Dr. Muir saw her in January, 1935; she was feeling very well and looked healthy, though thin.

The husband was born at Methil, Fife, in 1896. His father died of cerebral haemorrhage. His mother died in 1924, and a sister died in 1914, both of pulmonary tuberculosis. These deaths occurred at home, and have been verified by reference to the records of the Tuberculosis Service, Fife County. Mr. T. was healthy as a schoolboy. He joined the Army in 1915 and was fit for service until 1918, when he contracted malaria in Salonica, and at the same time began to cough. He left the service, but rejoined in 1922, and in 1925 was not allowed to proceed

to India on account of coughing. He stated that he had a cough when he married in 1923. He was first recognized as suffering from pulmonary tuberculosis in 1929, when he was discharged from the Army. Between 1925 and 1929 he was continually reporting sick.

Afterwards he lived with his family in Gillingham, and in 1930 while his wife was in one sanatorium he was in another. As the husband's home county was Fife the local authority arranged the transfer of the whole family to the county of Fife. Here he was visited by one of us (W. T. M.) and found to have extensive bilateral pulmonary tuberculosis with abundant sputum, which, as already stated, contained tubercle bacilli of the bovine type culturally, but atypical in virulence.

The child from whose gastric lavage the virulent bovine culture was obtained was the youngest of the three, aged 6 years. Tiny glands could be felt in his posterior triangles, and palpation of the abdomen gave the sensation of enlarged mesenteric glands. The spleen was not enlarged. There was a little cough, also slight systemic disturbance, and an x-ray film showed definite root infiltration on both sides.

The eldest child, a girl of 10, had small cervical glandular enlargements, and reacted positively to tuberculin, but showed no other evidence of tuberculous disease.

The remaining child, a girl of 8, was thin and showed slight enlargements of cervical glands, especially in the posterior triangles. The lungs gave an impaired note at left root, and an x-ray film suggested root infiltration. The reaction to tuberculin was pronounced. Gastric lavage was done on three occasions and the deposits tested on guinea-pigs for tubercle bacilli with negative results. All the children improved in the sanatorium and are now in good health.

BACTERIOLOGICAL INVESTIGATIONS

These have been extensive, and in this paper only a summary can be given. Five specimens of sputum from Mrs. T. and three from Mr. T. have been examined. Microscopically tubercle bacilli were numerous, and, as already stated, were beaded and vacuolated, and for the most part fairly long. A culture was obtained directly from each specimen, and the eight strains were found to be identical culturally one with another and with those bovine tubercle bacilli which grow with most difficulty on glycerin media (bovine Class I).

The virulence of the strains was tested by the inoculation of cultures into three young goats, fifteen rabbits, and fourteen guinea-pigs. The goats were inoculated intramuscularly, two with a strain from Mrs. T. (doses 10 and 20 mg.) and one with a strain from Mr. T. (dose 10 mg.). They were killed 147, 153, and 153 days after injection respectively, and each showed caseo-calcareous retrogressive tuberculosis at the seats of injection and adjacent prescapular glands and a few minute calcareous foci in the mediastinal glands; in addition, the lungs of one of the goats contained a moderate number of miliary tubercles. Only in the last goat were the disseminated lesions definitely more extensive than those which in this species follow similar injection of human tubercle bacilli. The rabbits were injected either intravenously or subcutaneously, and all except two, in which the disease was localized, showed, when examined after death, generalized tuberculosis more widespread than after similar injection of human bacilli, but less acute, except in one instance, than after standard bovine bacilli.

The guinea-pigs were injected either intraperitoneally or subcutaneously. They all lived longer, and showed, on post-mortem examination, a less severe form of generalized tuberculosis than guinea-pigs similarly inoculated with standard bovine or human tubercle bacilli.

The investigations in these two cases have shown that the tubercle bacilli from each person are typically bovine in cultural characters, but fall distinctly below the standard of the type in virulence for the goat, rabbit, and guinea-pig. The experiments on animals have not shown clearly that there is a difference in virulence between the strains from the two persons.

On the other hand, there are decided differences between the strains obtained from the parents and that from one of their children. The latter strain, obtained from a gastric lavage, is dysgonic—but not so dysgonic as those of the parents—and of full bovine virulence.

A goat inoculated intramuscularly with 10 mg. of the culture died in forty-two days of general miliary tuberculosis, the lungs being closely beset with tubercles. Two rabbits inoculated intravenously, doses 0.01 mg., died of severe general miliary tuberculosis in twenty-two and thirty days. Two guinea-pigs inoculated intraperitoneally died of acute general tuberculosis in eighteen and nineteen days, and two inoculated subcutaneously of general tuberculosis in thirty-eight and forty-three days.

Summary and Discussion

We have given the histories of two families, in each of which occurred two cases of phthisis pulmonalis in adults and in one, in addition, a case of glandular tuberculosis in a child, and we have stated the bacteriological evidence which establishes that all five cases were infected with tubercle bacilli of the bovine type. In one family the bacilli in the two cases examined were fully virulent. In the other the bacilli from the two cases were typically bovine in cultural characters, but fell below the standard of bovine viruses in virulence for the test animals, while the strain from the child was dysgonic and fully virulent.

We have now to consider the sources of the bacilli in the several cases. For each family there are three possibilities: (1) the persons with pulmonary tuberculosis acquired the infection through contact with human carriers of bovine tubercle bacilli (none of the patients came into direct contact with cattle); (2) all the cases were due to infection by ingestion—that is to say, through the consumption of cows' milk or milk products containing bovine tubercle bacilli; (3) one member of the family was infected by bovine bacilli through contact or through the milk and transmitted infection to the other (and to the child).

In the first family the mother had been a milkmaid, and was notified as a case of pulmonary tuberculosis when the two children who subsequently developed phthisis were 11 and 9 years old respectively. As the diagnosis in the mother was not confirmed by finding tubercle bacilli in her sputum, and the periods between her illness and the appearance of clinical signs in the children were very long, we do not think that either of the children was infected by the mother. The son showed clinical signs of tuberculosis some two years earlier than the daughter, but it is improbable that he infected his sister, since for many years they had not lived in the same house. The opinion that the girl—who died of pulmonary tuberculosis—was not infected either by her mother or her brother is supported by the necropsy findings, which indicated the alimentary tract as the channel of entry of the bacilli. It is highly probable that this was also the channel of infection in the brother, who was particularly fond of milk.

In the second family the facts are more complex. A sister and the mother of Mr. T. died of phthisis pulmonalis in 1914 and 1924 respectively. Unfortunately the mother was never under observation in Glenlond, and the type of bacillus in her case was not determined. We are unable to say, therefore, whether Mr. T. was probably infected by his mother or not. But if bovine bacilli were in fact transferred from mother to son the modification of virulence of the bacilli might possibly be the result of the prolonged residence in human tissues. There was nothing in his personal history to suggest that he might have been infected through milk. He was suffering from a cough in 1923, when he married, but was not notified as a clinical case of tuberculosis until 1929. His wife had pleurisy and an indefinite illness in her teens, but she was apparently well when she married and was not notified as a case of pulmonary tuberculosis until after the birth of her third child, in 1928. Her sister was notified in 1922 and

attended a tuberculosis dispensary, but she was now well, though thin. Thus in each case there is a family history of tuberculosis and a personal history suggesting infection before marriage. If bacteriological examinations had not been made no suspicion need have arisen that one of the persons was infected by the other. But the occurrence in both cases of bovine bacilli identical culturally and exhibiting about the same degree of attenuated virulence strongly suggests familial infection, which we think was probably from the husband to the wife (on the assumption that the illness from which she suffered before marriage was not due to tuberculosis, or, if it was, that this first infection had been overcome). An alternative explanation is coincident attenuation of bovine bacilli in two persons, who were both infected with virulent bovine bacilli before their marriage. We think that familial infection is the more probable, since attenuated bovine bacilli in phthisis are rare: they have been found in only three other instances in upwards of 120 cases of pulmonary tuberculosis caused by tubercle bacilli of the bovine type.

With regard to the child the bacteriological evidence is against transmission of infection from one of the parents.

REFERENCE

- ¹ Walker, G.: *British Medical Journal*, 1934, i, 371.

THE ACUTE HAEMOLYTIC ANAEMIA OF LEDERER

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Since Lederer¹ attempted a correlation of cases under the above heading (1925 and 1930) sporadic examples of this condition are found in the literature, mainly American. Parsons and Hawksley,² however, have reported nine cases in children, for the inclusion of which there appear to be very adequate grounds, despite the doubts cast by O'Donoghue and Witts³ on the wisdom of including examples occurring in children and in pregnant women.

We think that this is one of the most important of the smaller classes of recently recognized anaemias, in view of (1) its amenability to treatment, and (2) the possible confusion with pernicious anaemia and infective endocarditis; thus valuable time is lost in giving the necessary treatment—namely, blood transfusion.

The aetiological factors are still unknown, the problem presented both clinically and haematologically being that of a febrile haemolysis of rather acute onset. The presence of pyrexia has been supposed by most writers to indicate that the basic cause must be an infection. It has seemed to us, however, that the extremely rapid haemolysis and regeneration of blood would, of itself, suffice to account for the pyrexia; while the dramatic, almost critical, fall of temperature which follows a relatively small transfusion cannot well be explained on an infective basis.

Four cases have come under our care during the routine of hospital practice in eighteen months, the details of which we will summarize before adducing the criteria on which this diagnosis should be established.

CASE I

A hospital porter, aged 21, was noted on May 8th, 1933, to have become appreciably paler during the few days prior to examination. There was no history of any previous serious ill-health, while the family history was good. No drugs had