PUBLIC HEALTH ASPECT OF TUBERCULOSIS IN DOMESTIC ANIMALS*

BY

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The first advice to take interest in animal diseases came from Hippocrates, the Father of Medicine, who frequently refers to the usefulness of comparative pathology in its application to human medicine. He tells us that his observations on the hydatid cysts in the brain of goats helped him to use this information to combat the prevalent idea that human epilepsy was produced by demons. I shall not be able to change your views to such an extent; I hope only to contribute to a better understanding of the comparative pathology in tuberculosis.

It is difficult to deal with the comparative pathology of tuberculosis and with the possibility of mutual infection of animals and man without saying something about the history of tuberculosis in animals. Although tuberculosis in man is a disease of great antiquity and tuberculous lesions were found in the bones of Egyptian mummies, there is no clear evidence suggesting that tuberculosis existed in animals at the same time. Some old manuscripts mention the diseases of lungs in cattle, but we do not know whether they refer to pleuropneumonia or to tuberculosis. Keppler (1649) and Florini (1702) were the first to describe tuberculosis in cattle on a scientific basis. Of the various forms of tuberculosis in animals so-called pearl disease in cattle long ago attracted general attention, and the regulations concerning meat inspection in various countries included it. The disease was generally accepted as a syphilis and was called "French disease."

The proper study of tuberculosis in cattle started in the eighteenth century, when town dairies began to supply the manufacturing towns with milk and the incidence of tuberculosis was high.

Effect of the Industrial Revolution

There is no doubt that the industrial revolution played a great part in increasing the prevalence of tuberculosis, not only in man but also in animals. This disease is almost unknown among native cattle in prairie regions of South America or in the Steppes of Russia, or among sheep in any country, but it increases in prevalence as the larger towns are approached and intimacy of contact with overcrowded towns becomes closer. During the first half of the last century some authors regarded pulmonary tuberculosis in man and in animals as identical, while others, particularly Virchow, disputed the occurrence of tuberculosis in animals altogether. According to his view the lesions in the lungs and serous membranes were sarcomata which might be considered identical with lymphosarcomata of man.

Later experiments have shown not only that tuberculosis is infectious but also that it is transmissible by means of injection or through inhalation. This was proved in 1868, but it was not until 1910 that the exact relationship of the human, bovine, and avian types of infection and the transmission from one species to another were fully understood.

Before dealing with the character of the disease in various animals I will make a few general remarks on transmission

and its results. The evidence supporting the widely accepted view that the chief route of infection in both man and cattle is via the respiratory tract has been challenged by various workers. They maintain that infection mainly starts in the intestinal tract and that the significance of the lung and regional lymph node lesions as an indication of the route of infection is not very convincing, since the tubercle bacillus could pass through the intestinal wall and localize in the pulmonary tissues without leaving any trace of its paths through the abdominal cavity. Edwards (1937) studied the role of alimentary infection in the calf naturally infected with the bovine type of *Mycobacterium tuberculosis* for a period of 12 weeks. Out of 36 calves, 34 reacted to tuberculin, and at necropsy a careful naked-eye examination of the mesenteric glands failed to show the presence of visible lesions, whereas tubercle foci were found in the thoracic glands and in the lungs of every calf that was affected.

Soltys and Jennings (1950) experiments on dissemination of tubercle bacilli in guinea-pigs showed that tubercle bacilli inoculated subcutaneously were present in various organs and in the urine and faeces after a few hours, depending on the number of bacteria inoculated. No gross or microscopical lesions were noted in kidneys or mesenteric lymphatic nodes in the first five days, although tubercle bacilli were present in these organs. These experiments support the view of workers that the lung and regional lymph node lesions are not indicative of the route of infection, but are only an indication of the different affinity of various tissues to different types of tubercle bacilli.

Cattle

In the great majority of cases bovine tuberculosis occurs as a localized disease in which the lesions are of chronic and slowly progressive type with much connective tissue hyperplasia, caseation, and a great tendency to calcification. Bovine tuberculosis is always caused by virulent tubercle bacilli of bovine type. Human and avian tubercle bacilli in bovines have rarely been found in naturally acquired tuberculosis. In respect to tuberculous lesions it appears that of all animals the cow is the one most comparable to the human being. Of all tuberculous lesions in cattle, infection of the udder is of the greatest importance from the public health point of view as bacilli are excreted in milk. Bovine tubercle bacilli may often escape in milk of tuberculous cows even when there are no detectable lesions in the udder.

Tuberculosis in the mammary gland of the human being is a very rare finding, in contrast to its high frequency in the cow. The constant and high degree of activity in the animal may be an influential factor.

It is gratifying that the situation concerning control of tuberculosis in cattle is improving very rapidly in this country. Of the total cattle population (10,047,000), 73% are tuberculin-negative, and registered as attested herds (see Table). The remaining 27% do not belong to attested herds, and there is no doubt that a certain number of animals among them are tuberculous.

Area Eradication Plan for Tuberculosis Attested Herds Scheme, 1950. Statement Showing the Position in Great Britain as at October 1, 1957

	Total Cattle on June 4, 1957. (Provisional Figures)	No. of Registered Attested Herds	Total Attested Cattle	Percentage of Total Cattle
England	7,176,000	102,969	4,751,000	66
Wales	1,076,000	36,213	985,000	92
Scotland	1,795,000	41,689	1,617,000	90
Total	10,047,000	180,871	7,353,000	73

Tuberculosis in Sheep and Goats

Sheep are apparently just as susceptible to the bovine type of *Myco. tuberculosis* as cattle, but it is rare indeed to find a case of bovine tuberculosis in sheep, whether in

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Britain or abroad, and it is difficult to escape the belief that the different picture is consequent upon their way of life, as they are never housed. Most of the cases of tuberculosis in sheep are due to the avian type (Griffith, 1925; Creech, 1940). While it is impossible to trace the source of infection, it seems logical to conclude that wild birds, which are frequently infected with avian tubercle bacilli, are responsible for avian tuberculosis in sheep.

The rarity of the disease in sheep is confirmed by the statistics of the Bureau of Animal Industry in the United States. Out of 17 million animals slaughtered, only two were condemned because of tuberculosis. Information concerning tuberculosis in goats is very scanty, and with one or two exceptions tubercle bacilli obtained from tuberculous goats have been of the bovine type. Experimentally, goats and sheep can be readily infected with bovine tubercle bacilli. In naturally occurring tuberculosis in sheep and goats lesions were observed in the liver, lung, spleen, and lymph nodes, and on the pleura and peritoneum.

Tuberculosis in Pigs

The incidence of tuberculosis in pigs is an indicator of the amount of tuberculosis in cattle, people, and poultry in a given community, because pigs are susceptible to human, bovine, and avian types of tubercle bacilli.

Tuberculosis of pigs due to the human type of infection is rather rare. Information concerning percentage of human types varies: Gerbert (1939), in his studies on typing tubercle bacilli isolated from 50 tuberculous pigs, demonstrated 33 cases caused by the bovine type, 5 by the avian type, 3 by the human type, and 9 by mixed infection of avian and bovine types.

When infection of pigs by the human type of tubercle bacilli is known the fact should be of interest to those concerned with the public health. If the dissemination of human tubercle bacilli is occurring in a community in sufficient numbers to produce tuberculous lesions in pigs, it is reasonable to believe that the source of such pathogens is a potential danger to human beings.

Natural infection of pigs with human tubercle bacilli, which often occurs in pigs kept on the farm attached to sanatoria, seldom results in more than localized tuberculous adenitis.

The bovine type of the tubercle bacillus is capable of producing in pigs more severe and more widely disseminated tuberculosis than either of the other two types of the organism. Early spread via the blood is an outstanding feature, with the result that miliary lesions are common in the lungs, liver, spleen, and kidneys, with involvement of the bones and joints. While the incidence of the bovine type of infection in pigs has steadily declined as tuberculosis is being eliminated from cattle, the incidence of the avian type is still high. Pigs may be infected either from tuberculous poultry or from wild birds. Tuberculosis in pigs caused by the avian type is predominantly a localized disease of the lymph nodes of the alimentary tract. However, the disease may become widely distributed, with involvement of the liver, spleen, lungs, and kidneys.

Hermansson (1939) demonstrated that water in which a meat inspector and workers dealing with tuberculous pigs had washed their hands produced tuberculosis in guinea-pigs in 11 samples out of 16; similar results were obtained with towels. These experiments clearly show that working with meat and organs of tuberculous animals entails a considerable risk both for those engaged in the slaughtering and for those examining the meat, and may explain the frequency of skin tuberculosis in meat inspectors and butchers. Tubercle bacilli are also often spread to clean carcasses by using the same knife as for examining slaughtered animals.

Tuberculosis in Horses

Almost all cases of tuberculosis in the horse are due to the bovine type, and about half of the strains are of reduced

virulence. A few cases of tuberculosis due to the avian type are on record, and one case due to the human type has been described by Griffith (1928a). No accurate figures concerning the incidence of tuberculosis in horses in this country are available. This is mainly due to the fact that horses slaughtered in this country because of old age, general disability, or illness are not examined by the veterinary surgeon or even by the sanitary inspector. Nieberle (1931) stated that in German knackeries between 1904 and 1924 0.14% of the horses were tuberculous. Magnusson (1944) reported that, in Sweden, out of 461,436 slaughtered horses in the years between 1921 and 1942, 433 were tuberculous. Statistics of the incidence of tuberculosis in horses in various countries of Europe show that the disease has been very rare in these animals. The disease is often insidious in its onset and protracted in its course, and may be clinically inapparent for a long time.

The chronicity of equine tuberculosis, the proliferative nature of the lesions with the formation of large tumour-like masses, the non-caseating character, and the difficulty of recovering acid-fast organisms are the main characteristics of tuberculosis in a horse. Equine tuberculosis has something in common with Boeck's sarcoid or sarcoidosis, and may even support the view that Boeck's sarcoid and all related lesions are a form of non-caseating proliferative tuberculosis. It is interesting that the tuberculin test in this highly resistant animal is less reliable than in the case of many cattle or pigs. The organs mostly affected include lungs, liver, spleen, and nasal mucosa. Many other organs have been reported from time to time as being affected in individual cases.

Tuberculosis in the Dog

Tuberculosis in the dog is relatively rare. The available figures are highly selective and mainly based on necropsy material. The incidence of tuberculosis in dogs in Great Britain varies between 4 and 6% (Lovell and White, 1941; Jennings, 1949). The disease is most common between 1 and 5 years of age and relatively rare in old dogs. The animal is equally susceptible to human and bovine strains of tubercle bacilli, but it is much more resistant than man or cattle. From the fact that after the experimental intravenous inoculation of moderate doses (0.001 mg. per lb. (0.0022 mg. per kg.) of body weight) lungs will show lesions while other organs often remain uninvolved, it is evident that the lung in the dog, as in most other animals, offers a good soil for the development of tuberculosis. According to most workers the human type occurs in nearly 70%, and bovine in 30% of cases. It is generally agreed that the dog often acquires tuberculosis from a tuberculous person in the household or in restaurants, hotels, workshops, etc. The organs most often affected are lungs 72%, liver 67%, pleura 49%, kidneys 48%, and peritoneum 32% (Hjärre, 1939). Serous membranes in general appear to be more often involved in the dog than in the cat or any other animal.

Many workers found that in the dog the tuberculin test, whether intradermal or subcutaneous, is of little value in the diagnosis of tuberculosis because the animal develops only a low and irregular degree of allergy.

Tuberculosis in the Cat

Cats have a strong resistance to infection with tubercle bacilli of human and avian type, but are susceptible to the bovine type. Although there are a few records of the human type isolated from cats, it is not possible to say whether mistakes were made during typing. Griffith (1926) considers that cats are sensitive only to the bovine type.

Cobbett (1926) and Kuwabara (1938) found cats resistant to the human type of tubercle bacillus. These workers' results were confirmed by me. I was able to infect a cat with a dose of 0.001 mg. of the bovine type, but failed to infect cats with a dose of 10 mg. of the human type. The incidence of tuberculosis in cats varies between 3.6 and 13%. As in the dog, most of the figures are highly selective and mainly based on necropsy material.

Available evidence indicates that in most instances the infection in cats has its portal of entry by way of the digestive tract. Milk containing bovine tubercle bacilli and consumed by cats is the obvious source of most infections in these animals.

Tuberculin reaction in the form of thermoreaction appears to be more reliable than intradermal reaction.

Tuberculosis in Birds

With the exception of pets such as the parrot and the canary, in which the human tubercle bacillus is sometimes encountered, tuberculosis in birds is caused by the avian type of *Myco. tuberculosis*. Practically all species of domesticated birds and wild birds are susceptible to the avian tubercle bacillus. Tuberculous lesions occur most often in the liver, spleen, intestinal wall, and bone marrow. Other organs, including the central nervous system, may also be affected.

Human beings have a high resistance to the organism of avian tuberculosis, and therefore every alleged case of avian tuberculous infection in man must be established by convincing evidence. Even though true avian tubercle bacilli are obtained from materials of human origin, one should be cautious in assuming that the organism was actually responsible for the morbid progress in which it occurred.

Captive Wild Animals

Griffith (1928b) points out that tuberculosis in warm-blooded animals living in the wild state is unknown, but, on the other hand, it is common in animals kept in zoological gardens and menageries. It is an interesting finding of Griffith (1928b) and Lovell (1930) that the proportion of attenuated strains of tubercle bacilli isolated from these animals is much higher than from human or bovine cases.

The Public Health Aspect

The numerous publications presenting evidence incriminating the bacilli of bovine tuberculosis as a cause of tuberculous infections of human beings need no comment. Pasteurization of the public milk supply is now almost universal, except for some rural populations. It is interesting to know that 72 out of 570 milk samples examined biologically by the Veterinary Investigation Centre, Cambridge, during 1957, contained tubercle bacilli. This need cause no surprise, as Cambridgeshire, the Isle of Ely, and neighbouring counties have a very small percentage of attested cattle. In spite of the great advances in control of tuberculosis in cattle, there will be a constant potential hazard so long as only a few infected animals exist.

The gains made in controlling bovine tuberculosis can be maintained only by recognition of the fact that constant vigilance is necessary. It must be realized that not only a tuberculous animal but also a tuberculous person infected with the bovine type may transmit the infection. There are many records of persons who infected herds of cattle. Magnusson (1941) reported an instance where in a herd of 74 cows that had been free from tuberculosis for seven years 49 reactors suddenly appeared. Infection was traced to a woman milker who had assisted on the farm for a few weeks and was later discovered to be suffering from open pulmonary tuberculosis of the bovine type.

The part played by ruminants other than cattle and horses in spreading infection is less certain, since it is not known how far they are potential sources of danger to man. In all probability the horse, sheep, and goat can be disregarded on account of the relatively slight incidence of the disease.

Dogs and cats, however, which are in such intimate contact with man, may be responsible for the dissemination of infection. The public health aspect of tuberculosis in dogs and cats must receive much closer consideration. We may anticipate that with the progress in eradicating tuberculosis in cattle the disease should automatically become extinct in

cats; but in the dog, on the other hand, the reduction of bovine infection will not influence the incidence of tuberculosis to the same extent. The predominant danger for the dog is the human being with an active pulmonary focus from which tubercle bacilli are disseminated in the sputum. For this reason it is important that, so far as is possible, the type of the bacillus responsible for canine cases should be typed.

Stableforth (1929) reported that in four out of six canine cases of tuberculosis there was a history of human infection. Herlitz (1939), carrying out an investigation on transmission of tuberculosis from dogs and cats to human beings, observed that only 13 out of 65 families who had owned tuberculous dogs were affected with tuberculosis. Evidence that infection had passed from animal to man was adjudged as probable in two cases only. Similar investigations were carried out by Hawthorne *et al.* (1957) in Glasgow. They examined not only animals living with tuberculous patients but also human beings living among tuberculous animals. They found nine significant cases of tuberculosis in 14 families living in contact with tuberculous dogs. The dogs and cats owned by 37 patients with active tuberculosis were examined for the isolation of *Myco. tuberculosis*. It was recovered from the alimentary tracts of two dogs and two cats.

In addition to these two large-scale investigations there are several small ones of sporadic cases of transmission of the disease from dogs or cats to man. Urwitz (1949) described five cases of tuberculosis in human beings all infected by one dog; De Kock and Le Roux (1956) recorded one case of tuberculosis contracted from a dog. Lewis-Jonsson (1946) described tuberculosis in a 3-year-old boy who was bitten on the forearm by a tuberculous cat. The wound started to heal, but after 23 days sores developed at one site of the bite. Further examination of the child revealed miliary tuberculosis in the lungs, and he died three and a half months after receiving the bite. These observations seem to indicate that tuberculosis in household animals must be regarded as a possible source of danger, and much more energy should be displayed in attempting to eliminate these cases and drawing attention to the risk of the dissemination of infection by dogs and cats. Unfortunately, at present very little can be done in preventing the spread of tuberculosis from the small animals to man. The following example illustrates the difficulty.

A cat was brought to the veterinary hospital for examination. On examination it showed the clinical picture of tuberculosis, confirmed by a strong positive tuberculin reaction. The owner of the cat was a mother of two children aged 2 and 6, and she was warned about the danger of having the animal in the house. She refused to allow the cat to be destroyed, and it was therefore handed back to her. This situation often occurs, particularly when the animal is a special pet of the family, and legally nothing can be done.

At present the control and prevention of animal diseases, so far as it affects the animal population, is vested in the Ministry of Agriculture and is under the direction of Government veterinary officers. But all questions referring to animal diseases in relation to human health are dealt with by the Ministry of Health in England and Wales and by the Department of Health for Scotland through local authorities. Neither of these health departments employs a veterinarian as an adviser on veterinary matters affecting public health in Great Britain, as is done in many countries on the Continent and in the United States. More and more stress is being placed on animal production; consequently as the density of the animal population increases the incidence of diseases transmissible from animals to man increases also. Therefore the medical and veterinary professions should work hand in hand.

However, let us hope and believe that tuberculosis in animals and man in this country will be reduced to a disease of minor importance, or perhaps to a disease of the past, such as pleuropneumonia in cattle and plague in man.

Perhaps I may fairly sum up by pointing to improvement of living conditions of man and animals as the most

important factor in the control of tuberculosis. Early diagnosis of the disease is of the utmost value. Mass radiography, substantially on a voluntary basis, is the medium in human medicine. Tuberculin-testing is the counterpart in the veterinary field, and voluntary measures are rapidly giving way to compulsion in relation to cattle. I think it is safe to say that the cattle of Britain will be free from this scourge before the people, but there will remain other animals to keep the disease alive in its various forms.

Summary

The proper study of tuberculosis among domestic animals started during the period of the industrial revolution, which played a great part in the increase of tuberculosis in man and animals, particularly in overcrowded towns. Although infection in both man and animals is via the respiratory tract and the alimentary canal, the lung and regional lymph-node lesions are not convincing evidence of aerogenous infection, as the tubercle bacillus can pass through the intestinal wall and localize in the pulmonary tissues without leaving any trace of its path.

Tuberculosis of cattle is nearly always caused by tubercle bacilli of bovine type; human and avian tubercle bacilli have rarely been found in cattle. At present, of the total of over ten million cattle in Great Britain, 73% are free of tuberculosis, and it is hoped that in the very near future tuberculosis will be completely eradicated from them. The part played by ruminants other than cattle and horses in spreading infection is slight, as they are rarely infected; but so long as only a few infected animals exist there will always be a hazard of infection.

Pigs are susceptible to human, bovine and avian types of tubercle bacilli, but the bovine type is most common. The incidence of tuberculosis in pigs varies from 10 to 15%. The poor sanitary standard of slaughterhouses and the handling of meat and organs of tuberculous animals present a considerable risk of infection for meat inspectors and slaughterhouse employees.

Dogs and cats are a great risk in the dissemination of tuberculosis. At present there is no legislation by which a tuberculous dog or cat can be removed from the family. Therefore it is suggested that a veterinarian should be attached to the Ministry of Health in order to advise on the diseases transmitted from animals to man.

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INDOLIC COMPOUNDS IN THE URINE OF SCHIZOPHRENICS

BY

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It has been known for many years that certain drugs, such as harmine, ibogaine, hashish, and mescaline, were capable of giving rise to hallucinations in doses which were not dangerous to life and produced only minor physical effects. More recently the range of hallucinants has been increased by the synthesis of lysergic acid diethylamide, medmain, adrenochrome, etc. These new drugs are much more active, and will give rise to a well-developed drug psychosis in doses not producing more than a very transient vasomotor or peripheral neurological discomfort. Osmond and Smythies (1952) and Hoffer *et al.* (1954) pointed out that all these drugs contained or could probably be easily converted into a chemical containing an indole nucleus. Woolley and Shaw (1954) also commented on the similarity of many of these substances to serotonin and on their ability to antagonize the action of serotonin on the arterial wall. On the other hand, most of these chemicals have another common factor—namely, an ethylamino or diethylamino side-chain directly attached to the benzene or pyrrole ring—so that the pharmacological evidence cannot unequivocally incriminate disordered indole metabolism as a cause of the hallucinations.

Turning to clinical evidence, Riegelhaupt (1956) found that there was an excess of a substance giving the glyoxylic reaction (Hopkins and Cole, 1901) in the urine of many more schizophrenics than in those patients suffering from other forms of mental disease. The glyoxylic reaction was at one time thought to be specific for tryptophan, but it is now known to be given by quite a number of chemicals containing an indole nucleus. For these reasons it seemed worth while to make a detailed study of the indolic compounds found in urines of schizophrenics and to compare them with those found in normal controls. This was made a practical possibility by the work of Dalgliesh (1955) and Jepson (1955). Their methods were combined and adapted in the following manner for the present investigation.

Experimental

From the first specimen of urine passed in the morning 200 ml. was collected. The creatinine was estimated by the method of King and Wootton (1956) and a concentrate made by the technique described by Dalgliesh (1955), except that the carbon was blocked with 8% *n*-octadecylamine. During the steam distillation under reduced pressure the temperature was not allowed to rise above 65° C., since higher temperatures made the semi-quantitative results less repeatable. This was particularly noticeable with indole compounds substituted in the benzene ring. The final concentrate was dissolved in 50% v/v mixture of isopropyl alcohol and water. The volume of this solvent was so arranged that the aromatic substances recovered from a volume of urine containing 100 mg. of creatinine were present in 1 ml. of the final concentrate. This concentrate does not keep for long without decomposition, even at -15° C., and so it was applied as soon as possible to sheets of Whatman's 3 MM filter paper 34 by 32 cm. The volume