Observations

ON

THE BOVINE TUBERCLE BACILLUS IN
HUMAN TUBERCULOSIS *

BY

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It is now thirty-one years since Robert Koch, at the London Congress on Tuberculosis, announced his conclusion that infection of human beings with bovine bacilli was so rare that it was unnecessary to take special measures to prevent it. That statement, which was strongly contested, set in train investigations in many countries into the susceptibility of human beings to bovine tuberculosis, investigations which are still being carried on, and, in consequence of recent findings, with renewed energy and interest. It is appropriate in this, the fiftieth anniversary of Koch's discovery of the tubercle bacillus, to review the bacteriological work of the past thirty years to see where we stand in regard to this pressing and difficult matter of bovine tuberculosis.

Koch's opinion that bovine tuberculosis was a negligible factor in human tuberculosis was based, not on experimental work with a large amount of human material, but chiefly on the alleged extreme rarity of primary intestinal tuberculosis in Germany. He argued in the first place that one can assume with certainty that a case of tuberculosis has been caused by alimentary only in those instances where there is evidence of primary infection of the intestines, and secondly, that if man is susceptible to the bovine type primary intestinal tuberculosis should be of common occurrence, in view of the abundant opportunities for the transference of bovine bacilli through consumption of milk. This argument overlooked the possibility that bovine bacilli can traverse the intestinal mucosa without leaving in that tissue any trace of their passage.

THE ROYAL COMMISSION OF 1911

In this country tuberculosis of alimentary origin was certainly not rare, as necropsy records clearly showed. For example, Still in England concluded that in 29.1 per cent., and Shennan in Scotland that in 28.1 per cent., of tuberculous children primary infection had taken place through the intestines. It was obvious that this important question could not be left in doubt, and a Royal Commission was appointed. Its report in 1911 showed conclusively that Koch was mistaken in assuming that human beings ran little risk from infection with bovine bacilli. This type of bacillus was found to be the cause, not only of benign and localized, but also of severe generalized and fatal forms of tuberculosis, such as tuberculous meningitis and phthisis pulmonalis. But though the danger of bovine tuberculosis was thus so clearly demonstrated, no insistent and general demand arose in the country for a milk supply free from the living germs of tuberculosis. The belief originating with Koch that bovine bacilli produced at most only a mild form of the disease gave rise to the dangerous doctrine that a few bovine bacilli in the milk were desirable for their immunizing value against the more prevalent human tuberculosis, and for this reason opinion was divided on the advisability of eliminating all tubercle bacilli from milk.

The cases examined by the Commission, being to some extent selected and derived from London hospitals only,

did not provide an accurate basis for inference as to the relative frequency and distribution of infection with the bovine and human types of bacilli. The inquiry was therefore continued by some of the investigators of the Commission (Eastwood, F. Griffith, and myself) with support from the Local Government Board and Medical Research Committee and Council, while in Scotland similar investigations were instituted by Mr. (now Sir) Harold Stiles. In recent years valuable contributions have been made by Munro, Blacklock, and Cumming.

RESULTS OF INVESTIGATIONS DOWN TO 1931

As last year in Edinburgh I summarized the results of English and Scottish researches I will on this occasion only repeat the main conclusions. These investigations have demonstrated beyond doubt that bovine infection is responsible for a considerable amount of human tuberculosis in Great Britain. The total number of human cases in England and Scotland in which the type of infecting organism had been determined down to the middle of 1931 was 2,825. These comprised 1,040 cases of phthisis pulmonalis examined during life, 464 necropsies on persons dying from various causes, and 1,321 cases of other forms of tuberculosis. Of the 1,321 cases of the non-pulmonary forms of tuberculosis—namely, cervical gland, bone and joint, genito-urinary, skin, and meningeal—466 (35.3 per cent.) were caused by infection with bovine tubercle bacilli. Of this number 365 were in children under 5 years of age, and of these 198 (54.2 per cent.) yielded bovine bacilli. In the later age periods the percentage of bovine infection progressively diminished. The number of cases in adolescents and adults, however, was by no means unimportant. In the English series, excluding the cases of phthisis pulmonalis and lupus, there were more than twenty-four persons over 16 years of age, some of whom died—namely, one of abdominal and general tuberculosis, two of tuberculous meningitis, and one of renal tuberculosis.

Of the different non-pulmonary forms of tuberculosis cervical adenitis gave the highest percentages of bovine infection—85.7 in England and 84.9 in Scotland in children under 5 years of age, and 45.7 for England and 73.6 for Scotland at all ages. Then follow lupus with 48.6 and 53.8 per cent. for England and Scotland respectively, meningitis with 30.1 per cent. for England, and bone and joint tuberculosis with percentages of 18 for England and 42.8 for Scotland. The examination of material obtained from necropsies has given percentages of 16.8 in an unselected series in England and 33.3 per cent. for Scotland.

PHTHISIS CAUSED BY BOVINE TUBERCLE BACILLI

In striking contrast to these figures for the non-pulmonary forms of tuberculosis are those for phthisis pulmonalis. Of 1,040 cases examined in England and Scotland only 2.3 per cent. were definitely attributable to bovine bacilli—0.8 per cent. of 492 cases in England and 3.6 per cent. of 548 cases in Scotland, not including one case in which human tubercle bacilli were also found. It is seen, therefore, that in phthisis pulmonalis, as in nearly all the other forms of tuberculosis, the percentage of bovine infection was higher in Scotland. These examples of phthisis of bovine origin, though relatively small in number, are very significant. Many of the patients gave a history indicating that they had been infected in early life through the alimentary tract. Six had had enlarged cervical glands removed by operation (incidentally these cases disprove the hypothesis that cervical gland tuberculosis of bovine origin in early life protects one from phthisis later), and others had had abdominal tuberculosis. These instances show conclusively, therefore, that persons infected in childhood with bovine tubercle

* Read in opening a discussion in the Section of Tuberculosis at the Centenary Meeting of the British Medical Association, London, 1932.

bacilli may in adult life develop phthisis pulmonalis due to this same bacillus, and may possibly spread bovine tuberculosis to other human beings and to animals through the agency of sputum.

One is now in a position to state that all the arguments advanced by Koch in support of his opinion that bovine tuberculosis is of little importance for man have been disproved.

DANGER AND INCIDENCE OF BOVINE INFECTION

It is clear that the bovine tubercle bacillus can produce all the different forms of clinical tuberculosis and can set up tuberculous lesions in every organ and gland indistinguishable from those caused by the common human tubercle bacillus. Moreover, the ability of the organism to produce the progressive and fatal forms, such as tuberculous meningitis and phthisis pulmonalis, though entering the body from the alimentary canal—a more difficult channel of infection than the respiratory tract, the usual channel for the human bacillus—shows that the bovine bacillus must have a virulence for man at least as great as that of the human type.

The statistics to which I have referred are based on results obtained over a continuous period of twenty years down to the middle of 1931, and with samples of human material gathered from widely separated localities in Great Britain. Every year during the twenty years which have elapsed since the Royal Commission pointed out the danger of a tubercle-infected milk supply cases of human tuberculosis of bovine origin have been discovered in various parts of the country. The Special Committee of the People's League of Health, in its survey of tuberculosis of bovine origin in Great Britain, estimated that about 2,000 deaths, mostly in children, are caused annually by the bovine tubercle bacillus, and that at least 4,000 fresh cases of bovine infection develop each year. The figures in my opinion underestimate the loss to the community in deaths and disease from this cause.

RECENT RESEARCH

In order to show how serious the menace of bovine tuberculosis continues to be at the present day I will give the results of some recent investigations. I have completed the examination of cultures of bacilli obtained from eighteen children who died this year from tuberculous meningitis, and of these strains six (33.3 per cent.) were of the bovine type. Two of the latter six children were 2 years old, one was 3, one was 5, one was 6, and one was 20; necropsies on two showed that the tuberculosis was of alimentary origin. I have also obtained strains of bovine bacilli from several cases of bone and joint and cervical gland tuberculosis in children, some of whom were under 2½ years of age. It is certain, therefore, that at the present time children are being infected with bovine bacilli which in years to come will produce in some of those who escape early acute fatal disease the most serious of all forms of human tuberculosis, both clinically and epidemiologically—namely, phthisis pulmonalis.

This statement is warranted by the results of sputum examinations which Munro and I in collaboration, and Cumming, have recently obtained. In Scotland we have this year discovered seven more cases of phthisis with only bovine bacilli in the sputum, making twenty-seven in all; and Dr. Cumming permits me to say that he has found altogether fourteen cases—twelve in the North of England and two in London—since he started his investigations in 1931. With my four the number of cases of bovine phthisis found in England is now eighteen. Of the forty-five cases twenty-nine were in women and sixteen in men.

MUTATION OF BOVINE TO HUMAN TYPE

The question may be asked whether the proportion of cases which one can by biological methods definitely attribute to bovine tubercle bacilli accurately represents the magnitude of the damage done by bovine tuberculosis, whether in fact some of the cases from which one obtains human bacilli may not originally have been caused by the bovine type. The possibility that bovine bacilli might change into human bacilli in the human body was first suggested by Lord Lister in 1901, but this conception exerted great influence only from the time when Behring and Roemer supported it on the ground of their experimental observations. The transmutation hypothesis has several distinguished adherents, notably Rabinowitsch, Calmette, and Much. As it has been the subject of correspondence recently in the *British Medical Journal* I have thought that it will be useful to discuss briefly the evidence for and against.

Numerous attempts have been made to change the type characteristics of tubercle bacilli by passage through the bodies of different species of animals. It may be said at once that all the experiments where particular care was taken to guard against contamination through casual infection with another type of bacillus have been uniformly negative. It is unnecessary to give details of these experiments, but I will mention a few of especially long duration to illustrate how persistently the different types of tubercle bacilli retain their special characteristics. Several strains of human bacilli were unchanged in cultural characters and virulence after residence in the bodies of calves for periods up to 512 days, and in two cows for 529 days and 2½ years. Bovine tubercle bacilli were passed through the bodies of chimpanzees, the experiment lasting 512 days, of dogs for a period of about three years, and of toads for nearly eight years, without any change occurring. Avian tubercle bacilli, typical in cultural characters and in virulence for fowls, have been recovered from the mammary gland of a goat six years after the animal was inoculated subcutaneously with a culture of this bacillus.

Although favourable conditions for the occurrence of mutation cannot be, or at least have not yet been, artificially contrived, it is possible that these may arise during the progress of a natural infection—for example, where bovine bacilli persist in the tissues of a human being into adult life, giving rise to chronic slowly progressive tuberculosis. If one assumes, as I think it is assumed by many, that all adult tuberculosis owes its origin to infection acquired in childhood, and that this primary infection is predominantly bovine, mutation seems the obvious explanation of the gradually diminishing frequency of the bovine type as age advances. There is, however, much clinical and pathological evidence against the view that all tuberculous infection dates from childhood, and bacteriological investigations have shown that infection in infancy, presumably too recent for mutation to have occurred, is largely with the human type of bacillus.

The lower proportion of bovine infections in adults than in children is explicable on other grounds. Bovine tubercle bacilli enter the body almost exclusively by way of the alimentary tract, and since milk is the vehicle of infection the proportion of cases due to bovine bacilli is highest in children, whose chief article of diet is, or should be, milk. Secondly, a certain number of bovine infections disappear before adult age is reached, as in children bovine bacilli may cause death from general tuberculosis or tuberculous meningitis; furthermore, many of the forms of tuberculosis to which they give rise are curable and the bacilli die out. The preponderance of human bacilli in phthisis pulmonalis, which is the

principal form of adult tuberculosis, is due to the fact that phthisis is usually caused by human bacilli which have been inhaled.

Assuming that bovine bacilli can become transformed into human bacilli in the human body one would expect, unless the change is abrupt and complete, to meet with intermediate forms. Now it has been found that strains of tubercle bacilli of human origin do not always correspond exactly either to the human or to the bovine type, though clearly belonging to the mammalian group. These atypical strains have been considered by those who uphold the doctrine of the convertibility of tubercle bacilli to be intermediate—that is to say, in a transitional stage between bovine and human. For the reasons which I have stated elsewhere this view is probably incorrect. They represent, in my opinion, merely temporary or quasi-permanent variants of one or other of the two forms; they retain characteristics of the types from which they have been derived, and are often capable of complete reversion to the original type.

While there is no certain evidence that bovine bacilli change into human bacilli during residence in human tissues, there is, on the other hand, plenty of evidence that these bacilli can retain their characteristic properties during the whole course of a case of tuberculosis. For example, bovine strains, typical in every respect or only slightly below the normal virulence, have been obtained from seventeen cases of lupus which had lasted from thirteen to fifty-two years (average twenty-two years) and from many cases of phthisis in the adult which dated back to childhood. It is just in the latter form of the disease that one would expect the conditions to be most favourable for mutation. There is therefore no direct evidence to support the view that bovine tuberculosis is responsible for more cases of human tuberculosis than can be ascertained by the ordinary bacteriological methods.

The position disclosed by the facts which I have presented is sufficiently serious—without exaggeration—to demand the greatest efforts to prevent the grave loss through death and disease from this cause, and to bring about the eventual extinction of bovine tuberculosis, not only for economic and agricultural reasons, but also in the interests of human health.

THE ROLE PLAYED BY BOVINE TUBERCLE BACILLI IN HUMAN TUBERCULOSIS*

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At the Congress on Tuberculosis in London in 1901, Koch, as a result of experiments conducted by him, together with Schütz, on cows, asserted that bovine tubercle bacilli were of virtually no importance for human beings. He abandoned this extreme standpoint later, but, in Washington in 1908, he still declared that, while he regarded it as necessary to combat bovine tuberculosis for sound agricultural and economic reasons, he did not desire to see this done in connexion with the battle against human tuberculosis without further grounds. As a result of Koch's initiative, and doubtless also because of the opposition which his point of view evoked among many physicians and investigators, studies of the types of tubercle bacilli occurring in man and animals have been carried on in all parts of the world. Among such studies special importance must be ascribed to those carried on by the British

Royal Commission, by the Reichsgesundheitsamt, and by Park and Krumwiede. I should like to mention also that Robert Koch himself evinced very great interest in the reports of the British investigators. Neufeld tells us that the Royal Commission's report lay open on Koch's desk when he left his institute for the last time. To-day, when the result of the many investigations to which I have referred is available, we can form a fairly dependable conclusion concerning the very practical problem of the importance of bovine tuberculosis for human beings.

THE BOVINE BACILLUS

First of all, it is to be emphasized that it has been possible since Koch's day to confirm thoroughly his opinion that bovine tubercle bacilli can be definitely distinguished from human bacilli by laboratory investigation, and that the characteristics of the types are essentially constant. This fact is of the greatest importance, since it gives us a sure basis for determining the danger which menaces human beings from bovine tubercle bacilli. If the view, still held by some writers, were correct, that the characteristics of type are not constant, and that the one type can metamorphose itself into the other, and, in particular, that bovine bacilli can change into human bacilli in the human body, we should be obliged at the very outset to abandon the attempt to form any judgement as to this source of danger, and to leave the question open as to whether, following the Behring theory, human phthisis pulmonalis is due in the last analysis to the drinking of milk infected with tubercle bacilli in the first few years of life.

In diagnosing types in the Robert Koch Institute we proceed to-day in the following manner:

We secure pure cultures from tuberculous specimens, so far as possible, by the direct method—using the antiformin process or the Loewenstein-Hohn method—and also at the same time by the inoculation of guinea-pigs. As medium for the first culture we employ the egg culture without glycerin, described by Dorset, and alongside it Lubenau's culture with an addition of serum. From the pure culture secured directly by the first method or by the inoculation of guinea-pigs we inoculate the so-called differential culture mediums—bovine serum with and without glycerin, glycerin-agar, glycerin broth. If the result is such a development of the strain as has been shown by the investigations of the Reichsgesundheitsamt and the British Royal Commission to be characteristic for the bovine type, the pathogenicity of the strain is tested on rabbits. We prefer here, following Oehlecker, intravenous inoculation with 1/100 mg. of glycerin broth culture, with which results are achieved more quickly than by subcutaneous inoculation. Along with this we employ a test worked out by Toda in my laboratory, in which three strains to be tested are compared with a bovine strain of known high virulence through intracutaneous inoculation of 1/100,000 mg. in all four legs of the same rabbit. Bovine strains of typical virulence give rise to especially great primary infections of the skin, and above all a caseous tuberculosis of the regional lymphatic glands. Human strains never do this. Through the above method one arrives quickly—at most in two months—at a definite conclusion.

The diagnosis of the type is always difficult if one has to do with bovine bacilli of greatly weakened virulence, such as not infrequently occurs in cases of so-called external tuberculosis of human beings, especially in lupus. But it has been possible for me, with only very rare exceptions, to reach a definite decision as to the type. I share the opinion of Stanley Griffith and Neufeld that intermediate forms between the two types do not exist, but rather that the tubercle bacilli strains described by Lydia Rabinowitsch and other authors as intermediate forms are merely variants of the one or other type, or else mixed cultures of both types.

After these preliminary remarks concerning the method of diagnosing types, I will now endeavour, basing on all

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