EXPERIMENTAL EPIDEMIOLOGY OF TUBERCULOSIS

The Route of Infection in Naturally Acquired Tuberculosis of the Guinea Pig

By MAX B. LURIE, M.D.

(From The Henry Phipps Institute, University of Pennsylvania, Philadelphia)

(Received for publication, March 3, 1930)

It is generally held that the route of infection of tuberculosis in man is, with infrequent exceptions, the lungs and the alimentary tract, the latter including the pharynx and its lymphatic structures. Numerous experiments more or less reproducing the supposed modes of infection by these routes in man have been performed, either by feeding animals tubercle bacilli or by introducing droplets, air or dust laden with tubercle bacilli more or less directly into their lungs. The disease produced thus has been characterized by extensive lesions of the cervical and mesenteric nodes, when the mode of infection has been alimentary and by lesions in the lungs and the tracheobronchial lymph nodes when the respiratory route has been used. For a review of the literature and renewed experimental studies in this field the reader is referred to the recent publications of B. Lange and his associates (1).

In the studies of the experimental epidemiology of tuberculosis conducted in the laboratory of The Henry Phipps Institute tuberculosis was acquired by normal guinea pigs living in the same cage or in the same room with tuberculous animals under conditions more nearly approaching natural infection in man. In these experiments 45 guinea pigs have acquired tuberculosis under different conditions of exposure. The detailed observations on each of these animals have been recorded in other papers (2). It seemed desirable to compare the type of lesion produced in these animals by the different modes of exposure.

Of these 45 guinea pigs, 27 have acquired tuberculosis by being exposed to tuberculous cage mates under the following conditions. Eleven were exposed in groups of 3 to 3 tuberculous cage mates in

"ordinary" metal cages with a pan as floor, upon which the food was placed and came into contact with the bacilli-bearing excreta from the tuberculous animals. Seven have acquired tuberculosis in the same type of cage under the same conditions except that they were less crowded, groups of 2 being exposed to 2 tuberculous cage mates. Five guinea pigs have acquired tuberculosis by being exposed in groups of 3 to 3 tuberculous cage mates in "special" cages, which differed from the ordinary cages in that the floor was $\frac{1}{4}$ inch wire-mesh, through which the faecal boluses fell into a pan lying 3 inches below. The food for these animals was placed in metal cups attached to the door and walls of the cage. Four guinea pigs were exposed, like the last group, in special cages, but were less crowded, groups of 2 being confined with 2 tuberculous cage mates. Eighteen guinea pigs have acquired tuberculosis by being exposed to tuberculous animals in the same room but not in the same cage.

These experiments have extended over the past 3 years. Of the 45 animals, the mesenteric and tracheobronchial lymph nodes of 35 were available for comparison.

In Fig. 1 the relative size of the tuberculous mesenteric and tracheobronchial nodes of each of these animals has been depicted by tracing their borders. They are grouped according to the conditions of exposure under which the tuberculosis was acquired.

It will be seen that the tuberculosis acquired by guinea pigs exposed to tuberculous cage mates in the more crowded ordinary cages, where the food was soiled with tubercle bacilli, is characterized by a great enlargement and an extensive tuberculosis of the mesenteric nodes. The tracheobronchial lymph nodes, on the other hand, are involved to a very much smaller degree. Occasionally, as in Guinea pig 1, the disease is limited to the mesenteric nodes. In no case is the disease of the tracheobronchial nodes equal to that of the mesenteric and, on an average, the latter are on cross section 3.6 times larger than the former. Here the route of infection is predominantly enteric although the affection of the tracheobronchial nodes would suggest that the respiratory route is not completely eliminated. It would appear that under these conditions of exposure tubercle bacilli penetrate into the system by both routes but the more intensive exposure to infection by way of the intestinal tract determines the more extensive tuberculosis of the mesenteric nodes.

Where guinea pigs were exposed under identical conditions but in less crowded ordinary cages the size of the mesenteric lymph nodes is again very much larger than that of the tracheobronchial nodes, but

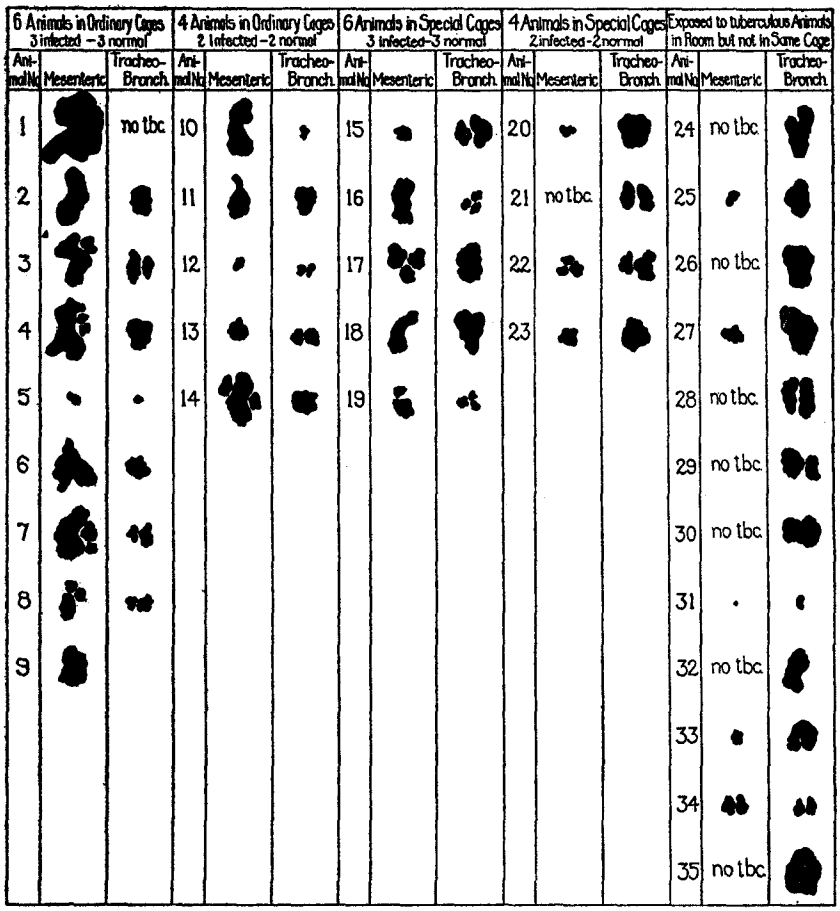

FIG. 1. The relative size of the mesenteric and tracheobronchial lymph nodes in contact tuberculosis of guinea pigs acquired under different conditions of exposure

the difference between the two groups of nodes is less marked, the mesenteric being 2.3 times instead of 3.6 times larger, as in the guinea pigs that acquired tuberculosis under more crowded conditions. In 2

out of the 5 guinea pigs, the extent of the disease is approximately the same in both groups of nodes. One may therefore say that in the less crowded ordinary cages the route of infection is again predominantly enteric but partly, and to a somewhat greater extent, respiratory.

Where guinea pigs were exposed in special cages with wire-mesh floors, to tuberculous animals, the excreta of which were largely eliminated from contact with the normal animals, the relative involvement of these two groups of nodes was reversed, namely, the tracheobronchial nodes were in some much more extensively tuberculous than the mesenteric. In 2 of the 5 guinea pigs that acquired tuberculosis in the very crowded special cages, the mesenteric nodes were involved to a greater extent than the tracheobronchial nodes; in one the affection was equal and in 2 the tracheobronchial nodes were affected to a greater degree. It is noteworthy that in these crowded cages considerable amounts of faecal material tended to become aggregated in the corners of the cage.

Thus in comparison with the tuberculosis acquired by cage mates exposed in similarly crowded ordinary cages, the disease acquired by the guinea pigs exposed in special cages was to a much greater extent of respiratory origin, although in some of the contacts in this group the disease was frankly enteric. Unfortunately, the results obtained with some of the more crowded cages, both the ordinary and the special, were complicated by the eating of tissue from dead tuberculous animals by the cage occupants. Nevertheless even in comparison with the tuberculosis acquired in the less crowded ordinary cages, where no eating of tuberculous tissue occurred, the disease acquired in the crowded special cages was still to a greater extent of respiratory origin.

Thus with the partial elimination of the enteric route of infection the respiratory route comes into prominence. This fact is more clearly brought out in the less crowded special cages where no eating of tuberculous animals occurred and where the contaminated excreta were almost completely removed. Each of the 4 guinea pigs that acquired tuberculosis in these showed a far greater affection of the tracheobronchial nodes than of the mesenteric. In one there was no tuberculosis of the mesenteric nodes in the presence of an extensive tuberculosis of the tracheobronchial; in another the affection of the former nodes

was negligible in comparison with the massive disease of the latter, and in 2 although the disease of the mesenteric nodes was considerable that of the tracheobronchial nodes was more extensive. On the average, the tracheobronchial nodes were 4 times larger than the mesenteric, a relationship directly the opposite of that seen in the crowded ordinary cages. Thus with a greater reduction in the intensity of exposure to enteric infection the bacillus penetrates largely by way of the respiratory tract.

The pulmonary disease in the guinea pigs that acquired tuberculosis in the special cages was more often extensive than that acquired in the ordinary cages. However no definite evidence of primary lesions in the lung in the former was found due to the dissemination of the disease at the time of death.

Where normal guinea pigs are kept in the same room but not in the same cage with tuberculous animals the tracheobronchial nodes in every case are massively affected. In 7 out of 12 animals that acquired tuberculosis under these conditions the mesenteric nodes were entirely free of macroscopic tuberculosis. In 4 there was a slight affection of the mesenteric nodes but a massive tuberculosis of the tracheobronchial lymph nodes. Here one may say that the route of infection is almost entirely by way of the respiratory tract and the amount of possible enteric infection, such as may be carried by the animal attendant from cage to cage, is negligible.

Associated with these lesions in the tracheobronchial lymph nodes, there was usually an extensive tuberculosis in the lungs frequently with excavation. In some there were lesions closely resembling human tuberculosis of the childhood type, one or several small nodules in the lung being accompanied by massive caseated tracheobronchial lymph nodes. This observation was possible as some of the animals died from intercurrent disease before the tuberculosis had become disseminated.

It is now generally accepted that tubercle bacilli may penetrate the intestinal mucosa without setting up any lesion at the site of entry, but usually the draining lymph nodes become extensively tuberculous. Amongst the guinea pigs that acquired tuberculosis by the enteric route in only 2 out of 27 was there any specific ulceration of the intestines, as revealed by a gross examination of the mucosa of the ileum

and that of the large intestines, and occasionally even the local lymph nodes failed to become tuberculous, as in Guinea pig 5. When tuberculosis develops by way of the respiratory route the lung is nearly always affected, but even here the tracheobronchial lymph nodes may be the seat of extensive tuberculosis without any macroscopic tuberculosis of the lung. Occasionally, as in Guinea pig 34, the reverse may be true.

SUMMARY AND DISCUSSION

Under conditions closely simulating the natural modes of tuberculous infection in man normal guinea pigs have acquired tuberculosis by being exposed under two degrees of crowding to tuberculous cage mates in ordinary cages, where the food became soiled with excreta, bearing tubercle bacilli, and in special cages, with wire-mesh floors, where this source of infection was almost entirely eliminated. Guinea pigs were also exposed in the same room but not in the same cage with tuberculous animals. It was found that the relative tuberculous involvement of the mesenteric and tracheobronchial nodes showed a gradation of change from an almost completely alimentary infection to a completely respiratory infection. The disease involved the mesenteric nodes predominantly in the crowded ordinary cages, with much less or no affection of the tracheobronchial nodes. It was similarly, but less markedly, enteric in origin in the less crowded ordinary cages, the mesenteric nodes again being larger than the tracheobronchial nodes, but the difference in size was not so great. In the more crowded special cages the relative affection of these two groups of nodes alternated, so that in some the mesenteric, in some the tracheobronchial nodes were more extensively tuberculous. A disease characterized by less or no affection of the mesenteric nodes and by extensive lesions of the tracheobronchial nodes was seen in the less crowded special cages. Finally there was a massive tuberculosis of the tracheobronchial nodes with usually no affection of the mesenteric nodes in the frankly air-borne tuberculosis acquired by guinea pigs exposed in the same room but not to tuberculous cage mates.

This gradation in the rôle played by the enteric and respiratory routes of infection, as first the one and then the other becomes the more frequent channel of entrance for tuberculosis, would indicate

that the penetration of tubercle bacilli by the one portal of entry inhibits the engrafting of tuberculosis in the tissues by way of the other portal of entry. It is apparent that in the special cages the opportunities for inhaling tubercle bacilli are at most equal to if not much less than in the ordinary cages; for in the latter dust from the bedding, laden with tubercle bacilli, is stirred up almost constantly by the animals, whereas in the special cages there is no bedding at all, and therefore, presumably, no more tubercle bacilli in the air than may occur in any part of the room. Nevertheless the route of infection was predominantly the respiratory tract in the special cages, especially in the less crowded, apparently because the enteric route had been largely eliminated. The greater predominance of the respiratory route amongst guinea pigs that acquired tuberculosis in the less crowded ordinary cages as compared to the lesser significance of this route in the more crowded ordinary cages would point in the same direction. These observations are in harmony with our knowledge that tuberculosis once implanted in an organism confers a certain degree of immunity to the disease. It is noteworthy that in a study of human autopsy material Opie (3) has found that when healed lesions are present in the mesentery focal tuberculosis in the lungs is seldom found, and that when first infection occurs by way of the lungs it tends to prevent the engrafting of the disease by way of the intestinal tract.

CONCLUSIONS

1. In tuberculosis of guinea pigs acquired by contact with tuberculous guinea pigs under conditions permitting the entrance of tubercle bacilli both by way of the alimentary and of the respiratory tracts, the type of lesion produced depends upon the relative intensity of exposure to infection by one or the other channel.

2. With the gradual elimination of exposure to alimentary infection tuberculosis is more and more completely engrafted through the respiratory route.

3. With the gradual increase in the intensity of exposure to alimentary infection, the disease becomes more and more completely enteric in origin.

4. Some evidence is presented that the engrafting of tuberculosis by

way of the alimentary route inhibits the development of respiratory disease.

BIBLIOGRAPHY

1. Lange, B., *Zeitschr. f. Hyg.*, 1924, **103,** 1; Lange, B., and Keschischian, K. H., *ibid.*, 1925, **104,** 256; Lange, B., and Nowosselsky, W., *ibid.*, 1925, **104,** 286,
2. Lurie, Max B., *J. Exper. Med.*, 1930, **51,** 729, 743, 753.
3. Opie, E. L., and Anderson, H., *Amer. Rev. Tuberc.*, 1920–21, **4,** 629; Opie, E. L., *ibid*, 1920–21, **4,** 641.