

EXPERIMENTAL EPIDEMIOLOGY OF TUBERCULOSIS

THE EFFECT OF ELIMINATING EXPOSURE TO ENTERIC INFECTION ON THE INCIDENCE AND COURSE OF TUBERCULOSIS ACQUIRED BY NORMAL GUINEA PIGS CONFINED WITH TUBERCULOUS CAGE MATES

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It was found by Perla (1) and confirmed in a previous paper (2) that guinea pigs exposed to tuberculous cage mates acquire a disease that is largely enteric in origin, the main source of contagion being the faecal matter of the inoculated animals. It was thought desirable to determine what effect if any would be exercised on the incidence and course of contact tuberculosis if normal guinea pigs are confined with tuberculous animals in a cage so constructed that the excreta do not remain in contact with the occupants or their food. Such a cage was devised.

It was made of metal, 14 inches in height and width and 15 inches in depth, with wire-mesh doors, like the cages used in the previous experiments except that, instead of a pan serving as a floor for the animals, the bottom of the cage was $\frac{1}{4}$ inch wire-mesh through which the faecal boluses fell into a pan lying 3 inches below. The food was placed in metal cups attached to the door and walls of the cage.

Methods

192 guinea pigs were separated into 4 groups of 48 each. Two groups were placed in the "special" cages described above. The other two groups were placed in ordinary cages like those used previously. In each cage type there were two degrees of crowding. One group of 48 guinea pigs was subdivided into 8 cages, 6 in each cage and a second group of 48 guinea pigs subdivided into 12 cages, 4 in each cage. Half of the animals in each cage were inoculated intraperitoneally with 0.001 mg. of the same strain of tubercle bacilli used in the earlier study (2),

and served as sources of contagion for the other half. There were thus 24 normal "contacts" in each of the 4 groups, distributed equally in two degrees of crowding in cages of two types. The population of all the cages was kept constant by replacing the dying animals, either the inoculated or the contacts, by similarly infected or normal animals. As with the previous study these experiments were continued for over a year.

Half of the contacts in each of the 4 groups were subjected to intracutaneous tuberculin tests beginning with the fourth month of the exposure and repeated at intervals of about 2 months thereafter, to determine if an animal once become sensitive to tuberculin will lose this sensitivity during the course of the exposure to the disease, and also to determine how long the disease lasted in those that eventually succumbed. The other half were left undisturbed. As controls for the air-borne tuberculous contagion of the room, 24 guinea pigs were subdivided into 6 cages, 4 plain and 2 special, each containing 4 animals and were left undisturbed during the course of the experimental period. The population of these cages was also maintained constant during this time.

Toward the end of the experiment all the surviving contacts and the controls for the room were tested twice with tuberculin at intervals of 1 month. If the result was positive the animal was isolated in a separate cage and observed until its death. Those that presented repeatedly negative tuberculin reactions were reserved for further study. Those that presented questionable reactions were killed and carefully autopsied. Animal inoculation and culture were also used in some cases to determine the presence of virulent or viable tubercle bacilli.

Results.—In the 8 ordinary cages, in each of which 3 normal guinea pigs were confined with 3 tuberculous animals, 7 developed tuberculosis. These data are summarized in Table I.

The experimental basis for judging the route of infection in these guinea pigs is given in a subsequent paper.

In Cage 2, Guinea pig 5 was exposed for the entire period of 370 days and died 449 days after the beginning of the experiment. The mesenteric lymph nodes are fibrocaseous and measure 25 x 15 mm. The mesenteric border of the intestines and the mesenteric vessels are studded with confluent nodular tubercles. The mucous membrane of the appendix is ulcerated. The tracheobronchial lymph nodes measure 15 x 12 mm. and are fibrous. There is a generalized tuberculosis of the lungs, liver and spleen. Acid-fast bacilli were demonstrated in the lung and in the mesenteric border of the intestines. The route of infection is undoubtedly enteric.

In Cage 4, Guinea pig 11 died on the 324th day of exposure. The nodes at the root of the mesentery form a huge matted fibrous mass with residual foci of caseation 40 x 26 mm. Many more mesenteric nodes are also extensively affected.

The cervical nodes, both the superficial and deep, show an extensive fibrocaseous tuberculosis. The tracheobronchial nodes measure 20 x 18 mm. and are fibrous. There are discrete tubercles in the lung and spleen and a pneumonia of the right

TABLE I

The Incidence of Contact Tuberculosis in Ordinary Cages Containing Three Normal and Three Tuberculous Guinea Pigs Each

Cage No.	Total No. of inoculated animals in cage during experiment	Total No. of contacts in cage during experiment	The three contacts that survived the longest period	Duration of exposure	Presence of tuberculosis in the contacts	Days survived by contacts that developed tuberculosis
1	17	4	1 D	289	none	
			2	370	none*	
			3 D	361	none	
2	16	5	4 D	297	none	449
			5 D	370	+	
			6 D	292	none	
3	23	3	7	370	none*	
			8 D	326	none	
			9	370	none*	
4	17	7	10	215	none*	324
			11 D	324	+	
			12	370	none*	
5	16	3	13	370	none*	
			14	370	none*	
			15	370	none*	
6	21	4	16 D	370	+	467
			17 D	370	+	440
			18 D	266	+	379
7	25	4	19 D	303	+	303
			20	370	none*	
			21 D	280	none	
8	21	3	22	370	none*	485
			23 K	370	+	
			24	370	none*	

D = died; K = killed.

* Absence of tuberculosis determined by repeated tuberculin tests.

lung, which was the cause of death. Acid-fast bacilli were demonstrated in the cervical nodes. The route of infection here is largely enteric.

In Cage 6, all the three contacts developed tuberculosis. Guinea pig 16 was exposed for the entire period and died 467 days after the beginning of the experiment. The mesenteric nodes are fibrous and enormously enlarged, measuring 50 x 20 mm., and showed acid-fast bacilli in a smear. No tuberculous changes were seen anywhere else in the body; the cause of death was fibrinous pleurisy. The route of infection is unquestionably enteric.

Guinea pig 17 was exposed the entire period and died 440 days after the beginning of the experiment. The tuberculous mesenteric nodes are 7 in number and fibrocaseous, the largest measuring 24 x 12 mm.; the superficial and deep cervical nodes are extensively involved and fibrocaseous. The tracheobronchial and other lymph nodes are moderately affected. There is a generalized, rather chronic type of tuberculosis in the spleen, liver and lungs with excavation in the latter. Innumerable acid-fast bacilli were demonstrated in the lungs. The route of infection is largely enteric.

Guinea pig 18 was exposed for 266 days and died 379 days after the beginning of the exposure. There is a massive, fibrocaseous tuberculosis of the mesenteric nodes, which measure 35 x 12 mm. The mesenteric border of the intestines is extensively involved by a confluent nodular fibrocaseous tuberculosis. The cervical, and other lymph nodes are extensively tuberculous. The tracheobronchial nodes measure 20 x 14 mm. and are fibrocaseous. There is a massive, somewhat fibrous type of tuberculosis in the spleen, liver and lungs, with cavities in the latter. Numerous acid-fast bacilli were demonstrated in the lungs. The route of infection is largely enteric.

Guinea pig 19 of Cage 7 died 303 days after the beginning of the exposure. The mesenteric nodes are small and contracted, with fibrocaseous foci. The cervical nodes are similarly affected. The tracheobronchial nodes show a single minute caseous lesion on each side. There is an extensive tuberculosis of the spleen, fibrosis in the liver and, in the lung, numerous tubercles, in which acid-fast bacilli were demonstrated. The cause of death was pneumonia. The route of infection is doubtful.

In Cage 8, Guinea pig 23 developed tuberculosis. It was exposed for 370 days and was killed 485 days after the beginning of the experiment. The mesenteric nodes are normal. Two cervical nodes measure 10 x 6 mm. and 8 x 4 mm. Each shows caseous foci. The tracheobronchial lymph nodes are enlarged and contain questionable tubercles. There are a few discrete tubercles in the lung, liver and spleen. Acid-fast bacilli were demonstrated in a pulmonary nodule. The infection was probably acquired by way of the pharynx.

The remaining 17 guinea pigs, exposed for a period of 215 to 370 days, failed to develop tuberculosis. As in the experiments of the previous year no direct correlation could be established between the total number of inoculated animals in a cage and the incidence of contact tuberculosis. Thus in Cage 6 the three contacts

exposed to a total of 21 tuberculous cage mates all developed tuberculosis but in Cage 3 none of the contacts developed tuberculosis although they were exposed to 23 tuberculous cage mates for the same length of time.

Unfortunately, in the more crowded cages, both the ordinary and the special, tissue from some of the sources of contagion was eaten by their cage mates before their death could be discovered. The evidence obtained from these two groups must therefore be regarded as diminished in value, although there was no constant correlation between this accident and the development of tuberculosis, and the results were amply corroborated by those obtained with the other two groups, the guinea pigs confined 4 per cage in 12 ordinary and 12 special cages, in which no tuberculous tissue was eaten.

Summary.—Of 24 normal guinea pigs in groups of 3 exposed in ordinary cages to 3 tuberculous cage mates for an average period of 339 days, 7 or 29 per cent developed tuberculosis. Of these, 1 was killed 485 days after the beginning of exposure; 3 died of an intercurrent infection with tuberculosis, and 3 died of tuberculosis alone. The route of infection was largely or wholly enteric in 5, probably the pharynx in 1, and doubtful in 1.

The disease was chronic in nature. In 3 animals there was little if any spread beyond the portal of entry; in 3 it was slowly progressive with healing in the liver or pulmonary excavation and in 1 the disease, though generalized, lasted for 9 months, as indicated by the tuberculin test. The average survival of exposure of those that died with tuberculosis was 394 days, ranging between 303 and 467 days.

Where 3 normal guinea pigs were confined with 3 tuberculous animals in 8 special cages, in which the ingestion of faecal material was greatly reduced, 5 developed tuberculosis. The data are summarized in Table II.

Guinea pig 8 of Cage 3 died 278 days after the beginning of the experiment. The mesenteric nodes are of normal size but fibrous. The tracheobronchial nodes are matted together, measuring 25 x 13 mm. and 17 x 7 mm.; both masses are caseous and encapsulated. There is an extensive fibrous caseous pneumonia of both lungs with occasional cavities, conglomerate tubercles in the spleen, discrete fibrous tuberculosis with healing in the liver and a generalized affection of the lymphatic system. Acid-fast bacilli were demonstrated in the lung. The route of infection here is the respiratory tract.

Guinea pig 17 of Cage 6 died 369 days after the beginning of the exposure. There is an extensive generalized tuberculosis of the lung, liver, spleen and lymphatic system. The mesenteric and tracheobronchial nodes are both extensively

involved. The latter are considerably the larger, fibrous and cartilaginous in hardness; the mesenteric nodes are fibrocaseous. Acid-fast bacilli were found in

TABLE II

The Incidence of Contact Tuberculosis in Special Cages Containing Three Normal and Three Tuberculous Guinea Pigs Each

Cage No.	Total No. of inoculated animals in cage during experiment	Total No. of contacts during experiment	The three contacts that survived the longest period	Duration of exposure	Presence of tuberculosis in the contacts	Days survived by contacts that developed tuberculosis
1	14	6	1	370	none*	
			2 D	240	none	
			3 K	309	none	
2	30	8	4 D	214	none	
			5 K	356	none	
			6 K	370	none	
3	14	10	7 D	118	none	278
			8 D	278	+	
			9 K	288	none	
4	13	10	10 D	370	none	
			11 D	328	none	
			12 D	211	none	
5	10	10	13 D	176	none	
			14 D	342	none	
			15 K	370	none†	
6	27	4	16	370	none*	369
			17 D	369	+	
			18	289	+	
7	19	7	19 D	163	+	163
			20 D	341	+	341
			21	370	none*	
8	17	11	22	370	none*	
			23 D	68	none	
			24	370	none*	

D = died; K = killed.

* Absence of tuberculosis determined by repeated tuberculin tests.

† Absence of tuberculosis confirmed by animal inoculation and culture.

the lungs. The route of infection is probably both the respiratory and the digestive tracts.

Guinea pig 18 of the same cage died after 289 days of exposure. The mesenteric nodes are a matted, fibrocaseous mass 25 x 15 mm.; the ileo-coecal nodes are similarly affected. The tracheobronchial and other lymph nodes are moderately affected and fibrocaseous. There are isolated tubercles in the lung and spleen. The cause of death was acute dilatation of the stomach. Acid-fast bacilli were demonstrated in the periportal nodes. The route of infection here is largely enteric. It is noteworthy that tissues from several tuberculous animals were eaten by the occupants of this cage.

Two deaths from tuberculosis occurred in Cage 7. Guinea pig 19 died 163 days after the beginning of the exposure. The lungs are consolidated by a pervasive fibrocaseous nodular tuberculosis. There is an extensive tuberculosis of the spleen and a fibrous tuberculosis of the liver. The tracheobronchial nodes are slightly enlarged and fibrous. The mesenteric and cervical nodes are moderately enlarged and fibrocaseous. Acid-fast bacilli were demonstrated in the lungs. The route of infection here is largely enteric.

Guinea pig 20 died 341 days after the beginning of exposure with an extensive generalized tuberculosis of the lung, liver, spleen, and lymphatic system. Both the mesenteric and the tracheobronchial nodes are extensively involved and fibrocaseous. Acid-fast bacilli were demonstrated in the lung. Both routes of infection were involved. In this cage again, tuberculous animals were eaten. But the tuberculosis of Guinea pig 19 could not be ascribed to this fact, for the eating occurred first on the 145th day of exposure only 18 days before the death of this animal from an extensive tuberculosis.

The 19 remaining contacts, exposed from 68 to 370 days, failed to develop tuberculosis.

Summary.—Of 24 guinea pigs in groups of 3 exposed to 3 tuberculous cage mates in special cages with wire-mesh bottoms for an average period of 293 days, 5 or 20.8 per cent died with tuberculosis. The route of infection in these animals was divided: in some it was largely or wholly respiratory; in others it was largely alimentary.

The disease was progressive in nature with little or no tendency toward healing. In 4 the tuberculosis was of an extensive generalized character; in 1 of them there was slight pulmonary excavation, but the animal succumbed 89 days after the disease was acquired. In 1 only had the disease spread little beyond the portal of entry, which was clearly the alimentary tract. The average duration of life was 288 days, ranging between 163 and 369 days.

Thus in these two groups the incidence of acquired tuberculosis in

TABLE III

The Incidence of Contact Tuberculosis in Ordinary Cages Containing Two Normal and Two Tuberculous Guinea Pigs Each

Cage No.	Total No. of inoculated animals in cage during experiment	Total No. of contacts in cage during experiment	The two contacts that survived the longest period	Duration of exposure	Presence of tuberculosis in the contacts	Days survived by contacts that developed tuberculosis
1	8	2	1	370	none*	353
			2 D	353	+	
2	10	2	3	370	none*	493
			4 K	370	+	
3	7	2	5 K	370	none†	454
			6 D	370	+	
4	9	3	7 D	236	none	
			8	370	none*	
5	8	2	9	370	none*	
			10	370	none*	
6	7	2	11	370	none*	
			12	370	none*	
7	4	2	13	370	none*	
			14	370	none*	
8	8	2	15	370	none*	439
			16 D	370	+	
9	6	3	17 K	370	none	280
			18 D	280	+	
10	8	4	19	315	none*	
			20 D	348	none	
11	6	3	21	288	none*	
			22	370	none*	
12	7	2	23 D	355	none	
			24 K	370	none**	

D = died; K = killed.

* Absence of tuberculosis determined by repeated tuberculin tests.

** Absence of tuberculosis confirmed by animal inoculation.

† Absence of tuberculosis confirmed by animal inoculation and culture.

the special cages was less than in the ordinary cages. The route of infection in the ordinary cages was largely enteric; in the special cages it was sometimes respiratory, sometimes enteric and sometimes both. In the ordinary cages the disease was distinctly more chronic than in the special cages; the contacts that acquired tuberculosis in these survived on an average 106 days longer than those in the special cages.

As noted above, the value of the data obtained for both these groups is problematical because of the eating of tuberculous tissue in some of the cages. However parallel results, unconfused by accidents, were observed in the other two groups, in which 2 normal guinea pigs were exposed to 2 tuberculous guinea pigs in ordinary and in special cages. The above data are therefore reported here as corroborative rather than as direct evidence.

When 2 normal guinea pigs were confined with 2 tuberculous animals in ordinary cages, 5 developed tuberculosis. The data are summarized in Table III.

In Cage 1, Guinea pig 2 died at the end of 353 days of exposure. The mesenteric nodes measure 27 x 14 mm. and are fibrocaseous. The tracheobronchial nodes are enlarged and fibrous. There is a generalized tuberculosis of a chronic type with pulmonary excavation. Numerous acid-fast bacilli were found in a smear from the lungs. The route of infection is probably both enteric and respiratory.

Guinea pig 4 of Cage 2 was exposed for 370 days and was killed 493 days after the beginning of the experiment. The mesenteric nodes are free of tuberculosis. The tracheobronchial and cervical nodes are enlarged and extremely fibrous. There are discrete tubercles in spleen, healed tuberculosis in the liver, and a small number of tubercles in the lung. Acid-fast bacilli were demonstrated in the tracheobronchial nodes. The route of infection is largely respiratory.

Guinea pig 6 of Cage 3 was exposed for 370 days and died 454 days after the beginning of the experiment. The cervical nodes are caseous; the mesenteric are enlarged and fibrous. The tracheobronchial nodes are negative. There is an extensive tuberculosis of the spleen, healing in the liver, and fibrous nodular pulmonary tuberculosis. The route of infection is alimentary.

Guinea pig 16 of Cage 8 was exposed for 370 days and died 439 days after the beginning of exposure. The mesenteric nodes are greatly enlarged and fibrocaseous, extending from the root of the mesentery to the hilum of the liver and measuring 37 x 12 mm. The cervical nodes are enlarged and fibrocaseous. The tracheobronchial nodes are small and contracted. There is an extensive chronic generalized tuberculosis of the lung, liver and spleen, with exudation into the pleural and peritoneal cavities. The route of infection is enteric.

Guinea pig 18 of Cage 9 died 280 days after the beginning of exposure from hemorrhage into the peritoneal cavity. All the lymph nodes are free of any gross tuberculous changes. The spleen is enlarged, with pin-point tubercles. There is a massive tuberculous bronchopneumonia; a smear of the lungs shows a pure culture of acid-fast bacilli. The route of infection is probably respiratory.

The remaining 19 guinea pigs exposed for 236 to 370 days failed to develop tuberculosis.

Summary.—Of 24 normal guinea pigs in groups of 2 exposed to 2 tuberculous cage mates in ordinary cages for an average period of 353 days, 5 or 20.8 per cent developed tuberculosis. The route of infection was clearly enteric in some, in others respiratory.

The disease was of a chronic nature with fibrosis, marked healing in the liver and sometimes pulmonary excavation. The 4 animals that died with tuberculosis survived an average of 381 days, ranging between 280 and 454 days.

Where 24 normal guinea pigs in groups of 2 were exposed to 2 tuberculous cage mates in the special cages, 4 developed tuberculosis. The data are summarized in Table IV.

Guinea pig 1 of Cage 1 died on the 261st day of exposure. The mesenteric nodes are hardened. There is an extensive fibrocaceous tuberculosis of the tracheobronchial nodes. There is a generalized tuberculosis of the liver, spleen and lungs with two cavities of pin-head size in the latter. Acid-fast bacilli were demonstrated in the lungs. The cervical and retrosternal nodes are fibrocaceous. The route of infection here is largely respiratory.

Guinea pig 7 of Cage 4 died from tuberculosis 282 days after the beginning of the experiment with massive, fibrous tuberculosis of the tracheobronchial nodes, which measure 24 x 15 mm. The mesenteric and cervical nodes are moderately enlarged and fibrocaceous; the former measure 15 x 12 mm., the latter, 15 x 8 mm. There is a generalized tuberculosis of the spleen, liver and lungs. The route of infection is mainly the respiratory tract. Acid-fast bacilli were demonstrated in the lungs and cervical lymph nodes.

Guinea pig 10 of Cage 5 died on the 212th day of exposure. There is a massive, caseous encapsulated tuberculosis of the tracheobronchial lymph nodes, which measure 27 x 27 mm. The mesenteric nodes present a single fibrocaceous focus. There is an extensive generalized tuberculosis of fibrous type in the lung, liver, spleen and lymphatic system. The lungs contain acid-fast bacilli. The infection has invaded the animal by way of the lungs.

Guinea pig 14 of Cage 7 died after 313 days of exposure. The mesenteric and cervical nodes are normal. There is an extensive fibrocaceous tuberculosis of the tracheobronchial nodes, an extensive fibrous nodular tuberculosis of the lungs,

TABLE IV
Incidence of Contact Tuberculosis in Special Cages Containing Two Normal and Two Tuberculous Guinea Pigs Each

Cage No.	Total No. of inoculated animals in cage during experiment	Total No. of contacts in cage during experiment	The two contacts that survived the longest period	Duration of exposure	Presence of tuberculosis in the contacts	Days survived by contacts that developed tuberculosis
1	12	3	1 D 2 K	261 370	+ none	261
2	7	4	3 4	215 370	none* none*	
3	8	2	5 D 6 K	351 370	none none	
4	13	5	7 D 8 K	282 206	+ none**	282
5	6	3	9 10 D	370 212	none* +	212
6	9	4	11 K 12 D	266 335	none† none	
7	10	4	13 14 D	370 313	none* +	313
8	9	2	15 16 D	370 370	none* none	
9	12	6	17 18 D	370 255	none* none	
10	8	2	19 D 20	370 370	none none*	
11	6	2	21 K 22 K	370 370	none none†	
12	6	4	23 24 K	154 370	none* none**	

D = died; K = killed.

* Absence of tuberculosis determined by repeated tuberculin tests.

** Absence of tuberculosis confirmed by animal inoculation.

† Absence of tuberculosis confirmed by animal inoculation and culture.

healing in the liver, and chronic, discrete tuberculosis in the spleen. The route of infection is respiratory.

Summary.—Of 24 normal guinea pigs exposed in the special cages in groups of 2 to 2 tuberculous cage mates for an average period of 319 days, 4 or 16.6 per cent died of generalized progressive tuberculosis with an average duration of life of 267 days, ranging between 212 and 313 days. In all of them, the route of infection was largely the respiratory tract.

Again, as was seen above in the more crowded cages, the incidence of contact tuberculosis in the special cages was lower than in the ordinary cages, but the severity of the disease was greater, the average length of survival being 267 days, or 114 days less than in the ordinary cages, where guinea pigs acquiring tuberculosis by contact lived an average of 381 days. Again, as in the more crowded cages, enteric infection played a prominent rôle in the genesis of the disease acquired in the ordinary cages, whereas in the special cages the disease was predominantly of respiratory origin.

That this longer survival of exposure in the ordinary cages is not due to the fact that the infection was contracted in these cages later in the course of the experiment but actually to a more slowly progressive disease is indicated by the following facts. Half of the contacts in each group were subjected to repeated tuberculin tests, and it was found that when sensitiveness to tuberculin was once established it was never lost. On this basis, data as to the time of onset of the disease were available for 9 out of the total of 21 contacts that developed tuberculosis in all 4 groups. Of these 9 contacts, 5 were in ordinary cages and 4 were in special cages. One of the 5 in the ordinary cages died of pneumonia. Of the remaining 8, the 4 guinea pigs in the ordinary cages lived 270, 150, 290 and 251 days, or an average of 240 days after the appearance of a positive tuberculin reaction, and the 4 guinea pigs in the special cages lived 89, 71, 137, and 87 days, or an average of only 96 days after the appearance of the positive tuberculin reaction. It can be said with certainty therefore, that when the alimentary canal as a route of infection is practically eliminated from cage contagion, a more acutely fatal form of disease is then acquired, chiefly through the respiratory tract.

Of the 24 guinea pigs that served as controls for the tuberculous contagion of the room 3 died with tuberculosis. It will be remembered

that they were distributed 4 per cage, 16 in ordinary cages and 8 in special cages. Two of the 16 in the ordinary cages and 1 of the 8 in the special cages died with tuberculosis. Two of the 3 died, in a good state of preservation, of intercurrent disease with tuberculosis after 321 and 324 days of exposure. The third died of tuberculosis on the 317th day of exposure. All 3 presented essentially the same pathological appearances: extensive or massive fibrocaseous or caseous tuberculosis of the tracheobronchial nodes, little or no tuberculosis in the mesenteric nodes, and a generalized, chronic type of tuberculosis with marked healing in the liver. Acid-fast bacilli were demonstrated in each animal. The route of infection in all these was clearly respiratory.

TABLE V

The Effect of Eliminating Enteric Contagion on the Incidence and Course of Tuberculosis Acquired by Normal Guinea Pigs Confined with Tuberculous Cage Mates

Degree of crowding	Cage type	No. of guinea pigs exposed	Average duration of exposure	No. developing tuberculosis	Percentage developing tuberculosis	Average survival in days of contacts dying with tuberculosis
6 per cage, 3 inoculated, 3 normal	Ordinary	24	339	7	29	394
	Special	24	295	5	20	288
4 per cage, 2 inoculated, 2 normal	Ordinary	24	353	5	20	381
	Special	24	319	4	16	267

SUMMARY AND DISCUSSION

In these studies normal guinea pigs were exposed to tuberculous cage mates in two different degrees of crowding, some in ordinary cages, where the food became contaminated with the excreta, laden with tubercle bacilli, of the inoculated animals, and some in special cages with wire-mesh floors, where these excreta were largely excluded as a source of contagion. The results are summarized in Table V.

In all these experiments crowding has always increased the incidence of the disease both in the ordinary and the special cages. However, due to the accident of eating of tuberculous animals in the more crowded cages these results are not conclusive, but they are in accord with the results of the previous study (2).

It was found that the incidence of tuberculosis was lower among the guinea pigs exposed to contagion in the special cages, in which little of the contaminated excreta remained in direct contact with the normal animals. In fact in the less crowded special cages the incidence of tuberculosis was only a little higher than among the same total number of guinea pigs exposed at the same time in the same room but not confined with tuberculous cage mates. In the special cages, especially in the less crowded, where nearly all the contaminated excreta were removed, the disease acquired was largely respiratory in origin and was characterized by an extensive tuberculosis of the tracheobronchial lymph nodes with little or no affection of the mesenteric nodes. The pulmonary disease in the guinea pigs that acquired tuberculosis in these 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. The tuberculosis acquired by the contacts in the ordinary cages, on the other hand, was usually enteric in origin, although both routes were involved, especially in the less crowded cages.

Moreover, a striking fact appears if we compare the course of tuberculosis in these two types of cages in both degrees of crowding: the contacts that developed tuberculosis in the ordinary cages survived an average of 106 and 114 days longer than the corresponding animals in the special cages.

It is well known that the respiratory route is a far more dangerous avenue of infection in tuberculosis than the alimentary canal. This fact has again been clearly brought out in the recent studies of Bruno Lange and his associates (3), who have shown that although guinea pigs may occasionally be infected by way of the mouth with quantities as low as 0.000,001 mg. of virulent tubercle bacilli they often escape infection even when fed 0.1 mg. or more. On the other hand if guinea pigs are made to inhale even the smallest quantities of tubercle bacilli they regularly contract tuberculosis. Furthermore they have also shown that the alimentary infection produces a disease far more chronic in character than that acquired by the respiratory route. It would therefore seem that the more acute type of disease is acquired in the special cages because in these cages the respiratory route plays

by far the more important rôle whereas in the ordinary cages the disease is largely of enteric origin.

However, it appears that in the ordinary cages where the guinea pigs were constantly stirring up their sawdust or peat-moss bedding, laden with tubercle bacilli, there was an even greater opportunity for respiratory infection than in the special cages where there was no bedding at all and where most of the excreta were removed from immediate contact with the normal animals. That the respiratory mode of infection plays a rôle even in the ordinary cages was shown in a previous communication (2) as well as in this paper. In both studies it was found that only in the more crowded ordinary cages is the disease almost entirely of enteric origin but in the less crowded ordinary cages infection takes place by the respiratory tract as well, though to a smaller degree than by the alimentary.

It would therefore appear that in the ordinary cages both routes are open for infection but the relatively larger doses of tubercle bacilli ingested determine a disease of enteric origin and hence of a chronic nature, suppressing at the same time the engrafting of the disease by way of the lungs, and that in the special cages where the alimentary sources of infection have been reduced to a minimum, the disease is engrafted by way of the lungs and is therefore of more acute type. Although in the special cages the intensity of exposure even to tubercle bacilli entering by the respiratory tract is less than in the ordinary cages, nevertheless the disease so produced is more acute, presumably because the inhibitory or retarding effect of enteric infection upon the development of respiratory disease is absent.

This explains the paradoxical effect observed of a greater incidence and a more chronic type of disease in the ordinary cages and a lower incidence and a more acute type of disease in the special cages, for the intensity of exposure by both routes is greater in the ordinary cages, and of the two, much greater by the enteric route.

CONCLUSIONS

1. If normal guinea pigs are confined with tuberculous cage mates in cages where the food becomes contaminated with the excreta, laden with tubercle bacilli, of the inoculated animals, the incidence of acquired tuberculosis amongst them is greater than amongst guinea

pigs similarly exposed in cages where this mode of infection is largely eliminated.

2. The disease acquired in the first type of cage is largely of enteric origin and is chronic in type.

3. The disease acquired in the second type of cage is of respiratory origin and has a more acute course.

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