EXPERIMENTAL EPIDEMIOLOGY OF TUBERCULOSIS

THE EFFECT OF A PRIMARY INFECTION ON CONTACT TUBERCULOSIS IN RABBITS

BY MAX B. LURIE, M.D.

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

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A study has been made of rabbits vaccinated with living tubercle bacilli of human type and subsequently exposed to tuberculosis under conditions simulating the natural modes of human contagion. In view of the present world-wide study of the prophylactic inoculation of human beings with BCG and other vaccines, the desirability of a method by which the safety and efficacy of a given procedure can be tested in small laboratory animals is obvious. The method employed in the present experiments can be used to throw light upon this and other problems in tuberculosis.

That conclusions drawn from inoculation experiments are not directly applicable to infection under natural conditions has been shown in the extensive experience of the last two decades with the vaccination of cattle. Although cattle treated with the bovovaccine of von Behring resisted for several months fatal doses of tubercle bacilli of bovine type introduced artificially, these animals nevertheless acquired tuberculosis when stabled for a year or more with cattle scattering tubercle bacilli (1). On the other hand it has been shown (2) that the laborious process of exposing experimental animals to tuberculosis by contact presents a much closer analogy to the disease as it occurs naturally in man.

The original observations of Robert Koch, showing that guinea pigs and rabbits acquire tuberculosis by contact with tuberculous animals, has found wide confirmation (3) in recent years. In the laboratory of The Phipps Institute, investigations on contact tuberculosis in the guinea pig (2) have clearly distinguished infection acquired by way of the alimentary, and by way of the respiratory tract, and showed that the route of infection depended on the relative intensity of exposure by one or the other channel (2).1 As in man, the engrafting of tuberculosis

1 Lurie (2), 1930, page 769.
by the alimentary route inhibits the development of respiratory disease. Again as in man, alimentary tuberculosis in the guinea pig runs a more chronic course than the respiratory infection (2). Furthermore the incidence of contact tuberculosis was greatly increased by crowding, a factor of great importance in the epidemiology of the disease among human beings. These points of similarity were offset, however, by the fact that in guinea pigs the incidence of tuberculosis is low when acquired by contact, especially when acquired by way of the respiratory tract.

In the present experiments, rabbits have been used. It was thought that in this animal the incidence of tuberculosis under the same experimental conditions might be higher than in the guinea pig. It has been shown (2) that the determining factor in the effect of crowding upon the incidence of tuberculosis is the amount of bacilli available for contagion. In the rabbit the kidney is one of the favorite sites of tuberculosis, with frequent involvement of the medulla, and excretion of large numbers of tubercle bacilli in the urine. Moreover the great difference in the susceptibility of this animal to tubercle bacilli of human type on the one hand, and of bovine type on the other, provided a method by which a primary lesion produced by vaccination with the less virulent type could be definitely distinguished from a lesion acquired by contact with tuberculous animals. By this means, also, tuberculosis characteristic of white adults could be imitated.

It is generally admitted that adult type tuberculosis in the European races is an exogenous or endogenous reinfection following the primary infection of infancy and childhood. A localized, non-progressive infection with living human type bacilli in rabbits might serve experimentally, therefore, as a primary lesion comparable to that acquired by man during childhood. If rabbits so treated, and then exposed to cage mates infected with bovine type bacilli, were to develop progressive tuberculosis, the lesion could be identified by isolating the causative agent in pure culture and determining its type.

Preliminary experiments showed, as had been expected, that the incidence of contact tuberculosis in normal rabbits exposed to cage mates infected with bovine type bacilli was much greater than in guinea pigs similarly exposed. Rabbits exposed to cage mates infected with the human type bacillus did not acquire the disease. Accordingly the following experiment was begun.

Method

Metal cages were built, measuring 27 inches in width, 32 inches in depth, and 15 inches in height, and equipped with wire mesh doors. To increase the ventilation, a window, 6 by 8 inches, was cut out in the back of the cages 4 inches above

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2 Lurie (2), 1930, page 753.
3 Lurie (2), 1930, page 729.
the floor, and covered with wire mesh. Into each of 7 cages, 8 rabbits were placed upon a metal pan having an approximate area of 6 square feet. 4 rabbits were infected intravenously with 0.001 to 0.000,01 mg. of a highly virulent strain of bovine type tubercle bacilli, "Ravenel," and served as sources of contagion for the other 4 animals in the cage. 2 of the latter were normal half grown rabbits free from tuberculous infection. The other 2 were rabbits of similar age that about 2 months previously had been given a subcutaneous inoculation of 1.0 mg. of a virulent human type tubercle bacillus, No. P-15 B.

In these cages the normal and infected rabbits were exposed under identical conditions to infection both by way of the alimentary and respiratory tracts.

To determine whether normal and infected rabbits will acquire tuberculosis under conditions eliminating gross alimentary infection, another cage of the dimensions given above was divided through the middle by a vertical partition of galvanized iron soldered to the walls. A window, 25 inches in length and 8 inches in height, was cut into this partition 6 inches above the floor. This opening was covered with 1/16 inch wire mesh gauze soldered to its edges. 4 rabbits inoculated intravenously with 0.001 to 0.000,01 mg. Ravenel strain were placed upon a pan in one compartment of the cage. These served as sources of contagion for 4 rabbits placed in the other compartment, 2 normal, and 2 vaccinated with human type bacilli as described above. To increase the circulation of air from the sources of contagion to the contacts, a slit, 26 x 3 inches, was made in the solid metal door of each compartment, 4 inches from the floor in the door closing upon the sources of contagion, and 11 inches from the floor in the door closing upon the contacts. The air warmed by the sources of contagion rises upward, passes through the wire mesh screening into the compartment containing the contacts and passes out through the slit in the door of this compartment. This 8th cage was referred to as the "respiratory cage."

The pans on the floor of the cages were bedded with peat moss. Food in adequate amounts was placed upon them daily, consisting of hay, oats, and bread soaked in water, with fresh green vegetables twice a week. The cages were cleaned three times weekly on alternate days. In case of death of any animal from an intercurrent infection the cage was sterilized.

The population of these 8 cages was kept constant by replacing the dying animals, either the sources of contagion or the contacts, by similarly treated or normal animals.

The extent of tuberculosis in the inoculated sources of contagion was determined at their death. In some of these the urine from the bladder was stained for tubercle bacilli.

The experiment was continued for over 1 year. At the end of this time all the remaining contacts were killed and a careful autopsy was performed on each of them. A diagnosis of tuberculosis in "normal contacts" was invariably confirmed by numerous smears for acid-fast bacilli. In 1 animal the virulence of a pure culture obtained from the lung was the same as that of the Ravenel strain used to inoculate the sources of contagion. The tuberculous lesions of animals that had a
primary infection with human type tubercle bacilli before exposure was begun, were cultured for tubercle bacilli after sodium hydroxide treatment. Their virulence was determined by inoculating 2 rabbits intravenously with 0.01 mg. of these cultures or of cultures obtained from other animals, rabbits or guinea pigs, that had been injected with the lesions of the contact animal. In this way the lesions found in these contacts could be definitely ascribed either to exogenous reinfection with the bovine type bacillus or to endogenous spread from the primary lesion caused by the subcutaneous inoculation with the human type bacillus. In some rabbits both the residual primary lesion in the subcutaneous tissues and the lesion in the lungs were cultured and the virulence of each culture determined. In some vaccinated contacts the type of the bacillus in the tuberculous lesions was determined by the direct intraperitoneal inoculation into rabbits; if death from massive generalized tuberculosis and tuberculous peritonitis resulted in about 2 months the lesion was considered to have been caused by the bovine type bacillus. Sections for microscopic study were prepared from the lesions of all contacts that developed tuberculosis.

RESULTS

The Primary Lesion of Vaccination

Before considering the main results of the experiment it is of interest to follow the course of the primary infection in the vaccinated contacts.

About 1 week after the subcutaneous inoculation of 1.0 to 0.01 mg. of the human type strain, P-1-5 B, a subcutaneous nodule developed, varying in diameter from 9 to 19 mm. The skin overlying this nodule was usually not adherent. The nodule gradually enlarged and the draining lymph nodes became affected between the 2nd and 3rd week after inoculation. The nodule then became softened and fluctuating. In rare instances the lesion ulcerated through the skin, and with the discharge of the caseous pus the ulcer healed. Usually the subcutaneous lesions became thoroughly encapsulated in fibrous tissue and remained dormant, although they contained living virulent tubercle bacilli of the human type even 1 year after inoculation. In other cases they resolved and left no trace behind, or left a flat area of brownish pigmented tissue consisting of regressive epithelioid cells (4). In one instance the lesion became calcified. In most cases the lesion was completely localized and the affection of the lymph nodes was transitory. In other instances, small numbers of tubercles with inconspicuous caseous centers were found in the lung and kidney. Rarely one or several encapsulated pus pockets swarming with living tubercle bacilli were found in the lung. In 1 rabbit there was a lesion in the ileocecal junction containing virulent tubercle bacilli. In all these lesions the bacilli were of the human type.
Contact Tuberculosis in Vaccinated and Normal Rabbits: Protocols

In Cage 1, 2 normal rabbits and 4 vaccinated rabbits were exposed to tuberculous rabbits. Normal Rabbits.—N-1-9 was killed after 373 days of exposure. The appendix, ileocecal region, and mesenteric nodes were tuberculous. There was an extensive tuberculosis of the pleura with pearl formation. The omentum was tuberculous. Large encapsulated pus pockets with a moderate number of discrete tubercles were found in both lungs. The tracheobronchial lymph nodes were not affected. The right kidney was extensively, and the left slightly involved. N-1-1 was killed after 430 days of exposure to a total of 26 tuberculous rabbits. No gross or microscopic tuberculosis could be found, nor could tuberculosis be demonstrated by guinea pig inoculation from non-specific lesions in the lung of this rabbit.

Vaccinated Rabbits.—I-5 and I-4 died with tuberculosis after an exposure of 355 and 290 days respectively. In I-5 there was no primary lesion of vaccination; in I-4 there was a fibrous scar. I-5 showed tuberculosis of the appendix with advanced fibrosis microscopically. The mesenteric nodes were not grossly affected. Caseous nodes were found in the pleura. Both lungs showed a moderate number of discrete tubercles, some 10 mm. in diameter, some firmly encapsulated with crumby centers. There was a small number of tubercles in the cortex of each kidney. The cause of death was an intestinal infection. I-4 died with tuberculosis of the appendix and mesenteric nodes, and an extensive discrete and conglomerate tuberculosis consolidating both lungs. The tracheobronchial nodes were slightly affected. There were caseous nodes in mediastinum and pericardium. The kidneys and bone marrow showed an extensive tuberculosis. Intraperitoneal injection of the lesions from the lung and pleura of each of these contacts into 2 normal rabbits caused fatal generalized tuberculosis in 34 to 71 days. I-5-0 and I-5-5, exposed for 139 and 100 days respectively, showed no tuberculosis except at the site of vaccination, which contained tubercle bacilli virulent for guinea pigs.

In Cage 2, 5 normal and 4 vaccinated rabbits were exposed. Normal Rabbits.—N-5-2 and N-7-0 each developed a single pulmonary tubercle 7 and 5 mm. in diameter respectively after 92 and 97 days of exposure. Both were extensively caseated and contained numerous tubercle bacilli. The tracheobronchial nodes were enlarged in both contacts and in N-7-0 they contained tubercle bacilli. N-6 died after 210 days of exposure with tuberculosis of the cervical nodes and appendix. The mesenteric nodes were free of tuberculosis. The lungs were consolidated by a massive caseous pneumonia. The tracheobronchial nodes were slightly affected. There was tuberculosis of the pleura and kidney and extensive tuberculosis of the bone marrow. N-1-0 and N-7-5 showed no tuberculosis after an exposure of 320 and 95 days respectively.

Vaccinated Rabbits.—None acquired tuberculosis. I-1-1 and I-5-4 exposed for 310 and 128 days respectively, showed no tuberculosis except at the site of vaccination. I-1-3 and I-5-3 exposed for 243 and 129 days respectively, showed in addition slight pulmonary lesions. These lesions caused slight non-progressive tuberculosis 67 and 61 days after intraperitoneal inoculation into normal rabbits.
In Cage 3, 4 normal and 3 vaccinated rabbits were exposed. **Normal Rabbits.**

—N-6-6 developed a single centrally caseated tubercle 6 mm. in diameter containing numerous tubercle bacilli in the lower lobe of the left lung after 109 days of exposure. The tracheobronchial nodes were enlarged. N-8 died after 194 days of exposure to a total of 12 tuberculous rabbits with consolidation of both lungs by extensively caseated discrete tubercles, caseous tuberculosis of the tracheobronchial nodes, but no gross tuberculosis of appendix, mesenteric or cervical nodes. The pleura and mediastinum were tuberculous with pearl formation. Miliary tuberculosis was found in the omentum. The kidneys and bone marrow were moderately tuberculous. The disease of respiratory origin in this contact may be contrasted with the tuberculosis acquired by the enteric route by N-1-8, which was killed after 375 days of exposure to a total of 23 tuberculous rabbits. There was extensive tuberculosis with ulceration through the mucosa in the appendix and ileoceleal region, extensive caseous tuberculosis with liquefaction of mesenteric nodes, miliary tuberculosis of omentum, extensive tuberculosis of pleura and pericardium with pearl formation, and widespread discrete and conglomerate tuberculosis of the lungs with extensive caseation. The tracheobronchial nodes were not affected. The kidneys were slightly tuberculous. N-4-7 died after 136 days of exposure, of an intestinal infection. There was no gross tuberculosis.

**Vaccinated Rabbits.**—I-3 and I-6 developed an enteric infection limited to the appendix, ileoceleal region, and mesenteric nodes after an exposure of 383 and 242 days respectively. Pure cultures obtained from these lesions either directly or after preliminary passage through a guinea pig caused fatal generalized tuberculosis in normal rabbits in 24 to 43 days. Both contacts had residual lesions at the site of vaccination. I-4-0 was killed after 191 days of exposure. There was an isolated caseous focus 3 mm. in diameter in the ileoceleal region. The mesenteric nodes were not affected. An isolated caseated tubercle 8 mm. in diameter was found in the lower lobe of the right lung. The tracheobronchial lymph nodes were free of tuberculosis. There was extensive tuberculosis of the pleura with pearl formation. At the site of subcutaneous inoculation of 1.0 mg. of a human strain of tubercle bacillus, A-1-D, there was an encapsulated nodule 15 mm. in diameter. A pure culture obtained from this primary lesion caused slight non-progressive tuberculosis in rabbits; a pure culture isolated from the lung and pleura caused fatal tuberculosis in 34 and 36 days after intravenous inoculation of 0.01 mg. into rabbits.

In Cage 4, 4 normal and 4 vaccinated rabbits were exposed. **Normal Rabbits.**

—N-7-1 was killed after 98 days of exposure. There was an isolated focus 2 mm. in diameter in the ileoceleal region and one in the appendix, 1 mm. in diameter. Innumerable tubercle bacilli were found in the smear of the lesion in the ileoceleal region and also in the tuberculous mesenteric nodes. N-9 and N-4-0 died of massive, caseous pneumonia with caseation of the tracheobronchial nodes after 194 and 155 days of exposure respectively. Both had moderate to extensive tuberculosis of the kidneys, and N-4-0 had tuberculosis of cervical and mesenteric nodes.
and a specific lesion in the right testicle. N-6-1 was killed after 140 days of exposure. There were two extensively caseated tubercles 7 and 4 mm. in diameter in the upper lobe of the left lung. The tracheobronchial nodes were tuberculous. There was beginning tuberculosis of the pleura with pearl formation.

Vaccinated Rabbits.—I-3-9, killed after 182 days of exposure, is to be contrasted with N-6-1. There were two tubercles in the lower lobe of the right lung, 12 and 5 mm. in largest diameter, with discrete foci of caseation. The tracheobronchial nodes were not affected. There was a moderate tuberculosis of the pleura with pearl formation. From the encapsulated subcutaneous abscess at the site of vaccination a pure culture of tubercle bacilli of the human type was isolated. From the pulmonary lesion a pure culture of the bovine type was obtained after preliminary passage through a rabbit. An essentially similar lesion was found in the lung of I-6A, killed after 56 days of exposure, and a pure culture of the bovine type was isolated. I-1-7 and I-8 died after 195 and 375 days of exposure respectively. Both showed tuberculosis of the appendix and mesenteric nodes, and extensive tuberculosis of the pleura and mediastinum, with, in I-1-7, pearl formation and involvement of the pericardium. There was an extensive discrete and conglomerate tuberculosis of both lungs in these contacts, with involvement of the tracheobronchial nodes in I-1-7. The tuberculosis of the kidneys was extensive in both cases, with excavation in I-8. This rabbit also showed tuberculosis of the uterine horns, trachea, and knee joint. The cervical nodes and the entire lymphatic system of I-1-7 were extensively affected. The primary lesion of vaccination was calcified in I-8, and in I-1-7 there was a subcutaneous encapsulated abscess containing tubercle bacilli. A pure culture obtained from the lung and pleura of I-8 caused fatal tuberculosis in rabbits in 32 and 37 days. The pulmonary lesion of I-1-7 injected intraperitoneally into 2 rabbits caused fatal tuberculosis in 35 and 44 days.

In Cage 5, 3 normal and 4 vaccinated rabbits were exposed. Normal Rabbits.—None of the normal rabbits, N-2-3, N-4-1, and N-1-6, exposed for 53, 307, and 432 days respectively developed tuberculosis, although N-1-6 was exposed to a total of 23 tuberculous rabbits.

Vaccinated Rabbits.—I-7 died of an unknown cause after 270 days of exposure, having a few discrete caseous tubercles in both lungs. A rabbit injected intraperitoneally with these lesions had a single pulmonary tubercle when killed in 77 days. I-2-6 died of pulmonary congestion and edema after 217 days of exposure. There were no tuberculous lesions anywhere in the body. I-9 was killed after 56 days of exposure and an encapsulated lesion with central softening 10 mm. in diameter, was found in the lower lobe of the right lung. The tracheobronchial nodes were not affected. A pure culture obtained from the lesion after preliminary passage through a rabbit caused fatal tuberculosis in 27 days in 1 rabbit. I-10 was killed after 437 days of exposure. There were irregular foci in the appendix and several nodules in the mediastinum, one with caseation. The mesenteric nodes were free of tuberculosis. Pure cultures obtained from the appendix and the
mediastinum respectively after preliminary passage through a guinea pig caused fatal generalized tuberculosis in rabbits in 22 to 26 days. Lesions containing tubercle bacilli were found in both contacts at the site of vaccination.

In Cage 6, 5 normal and 4 vaccinated rabbits were exposed. Normal Rabbits.—N-6-2 was killed after 144 days of exposure. A single almost completely caseated tubercle, 5 mm. in diameter, containing innumerable tubercle bacilli was found in the upper lobe of the left lung. The tracheobronchial nodes were enlarged and tuberculous. N-4-2 and N-4-8 died after 125 and 218 days of exposure respectively. Both had a massive caseous pneumonia, in N-4-8 honeycombed with cavities. In both, the tracheobronchial nodes, pleura, and kidneys were tuberculous. In N-4-2 the cervical and mesenteric nodes and bone marrow also were extensively diseased. N-1-4 died after 163 days of exposure of a combined enteric and respiratory infection with tuberculosis of the appendix, ileocecal region, and mesenteric nodes, an extensive discrete and conglomerate caseous tuberculosis of both lungs, tuberculosis of the tracheobronchial nodes, pleura, kidneys, and bone marrow. N-7-8, killed after 59 days of exposure, showed no gross tuberculosis.

Vaccinated Rabbits.—I-2 died after 240 days of exposure. There was an extensive tuberculosis of the appendix and ileocecal region with ulceration through the mucosa. The mesenteric nodes were not affected. Extensively caseated discrete tubercles pervaded both lungs. The pleura and kidneys were moderately tuberculous. The primary lesion of vaccination persisted with its contained tubercle bacilli. A pure culture obtained from the lung of this rabbit was of the bovine type. I-1-4 was killed after 381 days, and I-2-7 died of pneumonia after 271 days of exposure. In both the primary lesion of vaccination had healed. I-1-4 developed a single pulmonary tubercle, 5 mm. in diameter, with discrete caseous foci. The tracheobronchial nodes were free of tuberculosis. I-2-7 had extensive tuberculous lesions with ulceration of the mucosa in the appendix and ileocecal region, and moderately tuberculous mesenteric nodes. Both rabbits had tuberculosis of the pleura. The contrast between the alimentary and respiratory infections in vaccinated rabbits is clearly seen. A pure culture obtained from the pulmonary nodule in I-1-4 was of the bovine type. The intestinal lesion of I-2-7 caused fatal generalized tuberculosis in 47 days. I-6-1 was killed after 56 days of exposure. There was no gross tuberculosis except at site of vaccination.

In Cage 7, 4 normal and 4 vaccinated rabbits were exposed. Normal Rabbits.—N-4-6, N-3, and N-4-5 died with massive caseous pneumonia and tuberculosis of the tracheobronchial nodes after 122, 203, and 274 days of exposure respectively. There was no gross tuberculosis of the mesenteric nodes. All had moderate to extensive tuberculosis in the kidneys and pleura. In N-4-6 the entire left lung was a pus-filled cavity firmly adherent to the pleura with complete obliteration of lobar structure. Numerous tubercle bacilli were found in the pulmonary lesions of all these rabbits and virulent tubercle bacilli were demonstrated in the pus of the left lung of N-4-6. N-7-2 was killed after 98 days of exposure.
was a moderate tuberculosis of both lungs with extensive caseation of the tracheobronchial nodes. The mesenteric nodes were not tuberculous. The pleura was moderately and the kidneys slightly tuberculous.

Vaccinated Rabbits.—I-5-7 was killed after 84 days of exposure. There was one caseous tubercle 8 mm. in diameter in the base of the left lung. I-3-2 died after 196 days of exposure of extensive pulmonary tuberculosis with excavation. The anastamosing lesions resembled the folds of the brain. The kidneys were moderately tuberculous. In neither contact were the tracheobronchial nodes affected. The subcutaneous lesion of vaccination in both contained numerous tubercle bacilli. Pure cultures obtained from the pulmonary lesions of each of these contacts after preliminary passage through rabbits were of the bovine type.

Vaccinated Rabbits.—I-1-8 died after 342 days of exposure with discrete and confluent fibrocaseous pulmonary tuberculosis, with foci of softening containing few tubercle bacilli; the tracheobronchial nodes were not affected. A few caseous nodules were found in the mediastinum. A pure culture obtained from the pulmonary lesion after preliminary passage through a guinea pig caused fatal generalized tuberculosis in rabbits in 44 days. I-5-2 and I-3-1, coming to autopsy after 126 and 97 days of exposure respectively had pulmonary and renal lesions, which caused slight, non-progressive tuberculosis on intraperitoneal inoculation into...
normal rabbits. These 3 contacts had residual primary lesions of vaccination, those in I-1-8 and I-5-2 containing tubercle bacilli.

**Incidence of Contact Tuberculosis**

In the above protocols are given the most significant data for each of the 30 normal and 30 vaccinated contacts used in these experiments. As is seen there, tuberculosis was acquired by some of the contacts, either the normal, the vaccinated, or both, in each of the 8 cages. The incidence and course of the acquired disease was not apparently different in the respiratory cage, No. 8, in which the contacts were separated from the sources of contagion by a fine, wire mesh screen, and in the remaining 7 cages, in which the animals were not separated. All the contacts are therefore considered together.

In Table I the significant data and conclusions relative to each of these rabbits are summarized. The contacts are listed in the order of increasing duration of exposure. To facilitate reference to the protocols the number of the cage in which each contact was exposed is given.

**Incidence in the Vaccinated as Compared with the Normal Contacts.** —It can be seen that out of a total of 30 normal rabbits exposed for periods varying from 53 to 432 days, with an average exposure of 200, and a mean exposure of 155 to 163 days, 22 or 73.3 per cent developed tuberculosis. Out of a total of 30 vaccinated rabbits exposed for periods varying from 56 to 437 days, with an average exposure of 218 and a mean exposure of 196 to 217 days, 18 or 60 per cent acquired tuberculosis. That the tuberculous lesions in these 18 rabbits were caused by bovine type bacilli was demonstrated by the virulence for rabbits of pure cultures isolated from them or by fatal generalized tuberculosis resulting in from 24 to 47 days, and in one instance in 71 days, after the direct intraperitoneal inoculation of these lesions into other rabbits. In the remaining 12 rabbits, either there were no lesions beyond the site of vaccination or there were tuberculous lesions in other parts of the body caused by endogenous spread from the primary lesion, as shown by the recovery from them of tubercle bacilli of human type. The incidence of acquired tuberculosis among these rabbits was thus definitely less, 27 per cent of normal rabbits, and 40 per cent of the vaccinated rabbits having escaped infection.
## TABLE I

The Incidence and Extent of Acquired Tuberculosis in Normal and Vaccinated Rabbits

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Case No.</th>
<th>Duration of exposure (days)</th>
<th>Extent of tuberculosis</th>
<th>Route of infection</th>
<th>Rabbit No.</th>
<th>Case No.</th>
<th>Duration of exposure (days)</th>
<th>Extent of tuberculosis</th>
<th>Route of infection</th>
</tr>
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<tbody>
<tr>
<td>N-2-3</td>
<td>5</td>
<td>55</td>
<td>0</td>
<td>+</td>
<td>I-6A</td>
<td>4</td>
<td>56</td>
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<td>Resp.</td>
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<td>0</td>
<td>+</td>
<td>I-9</td>
<td>5</td>
<td>56</td>
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<td>Resp.</td>
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<td>+</td>
<td>Resp.*</td>
<td>I-6-1</td>
<td>6</td>
<td>56</td>
<td>0</td>
<td>Resp.</td>
</tr>
<tr>
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<td>95</td>
<td>0</td>
<td>+</td>
<td>I-5-7</td>
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<td>84</td>
<td>+</td>
<td>Resp.</td>
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<td>+</td>
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<td>90</td>
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<td>Resp.</td>
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<td>Resp.</td>
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<td>Resp.</td>
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<td>Resp.</td>
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<td>Resp.</td>
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<td>0</td>
<td>Resp.</td>
</tr>
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<td>++++</td>
<td>Resp.</td>
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<td>Resp.</td>
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<td>Al., Resp.</td>
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<td>Resp.</td>
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<td>Resp.</td>
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<td>Resp.</td>
<td>I-4-0</td>
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<td>Resp.</td>
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<td>193</td>
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<td>Al., Resp.</td>
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<td>196</td>
<td>++++</td>
<td>Resp.</td>
</tr>
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<td>++++</td>
<td>Ent., Resp.</td>
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<td>Ent.</td>
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<td>++++</td>
<td>Resp.</td>
<td>I-6</td>
<td>3</td>
<td>242</td>
<td>+</td>
<td>Ent.</td>
</tr>
<tr>
<td>N-3</td>
<td>7</td>
<td>202</td>
<td>++++</td>
<td>Resp.</td>
<td>I-1-3</td>
<td>2</td>
<td>243</td>
<td>0</td>
<td>Resp.</td>
</tr>
<tr>
<td>N-6</td>
<td>2</td>
<td>210</td>
<td>++++</td>
<td>Al.</td>
<td>I-7-7</td>
<td>5</td>
<td>270</td>
<td>0</td>
<td>Resp.</td>
</tr>
<tr>
<td>N-4-8</td>
<td>6</td>
<td>218</td>
<td>++++</td>
<td>Resp.</td>
<td>I-2-7</td>
<td>6</td>
<td>271</td>
<td>++</td>
<td>Ent.</td>
</tr>
<tr>
<td>N-4-5</td>
<td>7</td>
<td>274</td>
<td>++++</td>
<td>Resp.</td>
<td>I-4-1</td>
<td>1</td>
<td>290</td>
<td>++++</td>
<td>Ent.</td>
</tr>
<tr>
<td>N-4-1</td>
<td>5</td>
<td>307</td>
<td>+</td>
<td>Resp.</td>
<td>I-1-1</td>
<td>2</td>
<td>310</td>
<td>0</td>
<td>Resp.</td>
</tr>
<tr>
<td>N-1-5</td>
<td>8</td>
<td>317</td>
<td>++++</td>
<td>Resp.</td>
<td>I-1-8</td>
<td>8</td>
<td>342</td>
<td>++++</td>
<td>Resp.</td>
</tr>
<tr>
<td>N-1-0</td>
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<td>320</td>
<td>0</td>
<td>+</td>
<td>I-5</td>
<td>1</td>
<td>355</td>
<td>+</td>
<td>Ent.</td>
</tr>
<tr>
<td>N-2-2</td>
<td>8</td>
<td>354</td>
<td>+</td>
<td>Ent.</td>
<td>I-1-5</td>
<td>7</td>
<td>362</td>
<td>++++</td>
<td>Resp.</td>
</tr>
<tr>
<td>N-1-9</td>
<td>1</td>
<td>373</td>
<td>+</td>
<td>Ent.</td>
<td>I-8</td>
<td>4</td>
<td>375</td>
<td>++++</td>
<td>Ent.</td>
</tr>
<tr>
<td>N-1-8</td>
<td>3</td>
<td>375</td>
<td>++++</td>
<td>Ent.</td>
<td>I-1-4</td>
<td>6</td>
<td>381</td>
<td>+</td>
<td>Resp.</td>
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<tr>
<td>N-1-1</td>
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<td>430</td>
<td>0</td>
<td>+</td>
<td>I-3</td>
<td>3</td>
<td>383</td>
<td>+</td>
<td>Ent.</td>
</tr>
<tr>
<td>N-1-6</td>
<td>5</td>
<td>432</td>
<td>0</td>
<td>+</td>
<td>I-1-0</td>
<td>5</td>
<td>437</td>
<td>+</td>
<td>Ent.</td>
</tr>
</tbody>
</table>

* Resp. = respiratory. Ent. = enteric. Al. = alimentary.
Incidence in Relation to Length of Exposure.—Unfortunately the tuberculin reaction in the skin of rabbits is not well marked, and x-ray examination of the lungs revealed only moderately advanced lesions. Hence the time of inception and the exact duration of the disease could not be determined. Still sufficient numbers of animals either were killed or died at different intervals of time so that a definite relation could be observed between the duration of exposure and the incidence of contact tuberculosis. If a rabbit failed to develop tuberculosis at the end of a certain interval it was supposed that it had not had the disease at a previous interval. For example, Rabbits N-4-1, N-4-0, N-1-1, and N-1-6, showing no evidence of tuberculosis when they were killed after 307 to 432 days of exposure, presumably had none after 100 or after 200 days of exposure, and in Table II they are included in each of the three intervals.

As can be seen from Table II, 33 per cent of normal rabbits acquired tuberculosis within the first 100 days of exposure. 66 per cent of normal rabbits acquired tuberculosis when exposed from 101 to 200 days. Further exposure of normal rabbits did not increase the incidence of the disease. Among the vaccinated animals 20 per cent acquired tuberculosis within the first 100 days of exposure. Of vaccinated rabbits exposed from 101 to 200 days 33 per cent developed tuberculosis as compared with twice that percentage of normal rabbits similarly exposed. However further exposure of the vaccinated rabbits resulted in a conspicuous increase in the incidence of the disease. It is noteworthy that the total incidence of tuberculosis among normal contacts exposed for a period up to 200 days was 63.6 per cent whereas only about half as many vaccinated contacts, 36.8 per cent, acquired the disease.

Incidence in Relation to the Number of Sources of Contagion.—It is evident that the length of exposure would be an exact measure of the quantity of tubercle bacilli to which the contacts were exposed if the elimination of bacilli were constant throughout the disease. Since, however, they are expelled chiefly in the later stages, it is significant that the incidence of acquired tuberculosis increased with an increase in the number of animals to which the contacts were exposed, as the sources of contagion that died of tuberculosis were replaced.

Vaccinated rabbits escaped infection after exposure to increasing
numbers of tuberculous rabbits to a greater degree than did normal animals, but again only up to a certain point. For although 3 normal rabbits, N-1-0, N-1-1, and N-1-6, escaped infection completely after having been exposed to a total of from 20 to 26 tuberculous rabbits during a period of 320 to 432 days, none of the 7 vaccinated contacts listed last in Table I escaped exogenous infection after having been exposed to a total of from 21 to 23 rabbits for a period of 342 to 437 days. Thus the contrast observed between the vaccinated and the normal contacts in the incidence of contagion in relation to length of exposure holds equally in relation to the number of tuberculous rabbits to which the contacts were exposed.

### TABLE II

<table>
<thead>
<tr>
<th>Duration of exposure</th>
<th>Normal</th>
<th>Vaccinated</th>
<th>Normal</th>
<th>Vaccinated</th>
<th>Normal</th>
<th>Vaccinated</th>
<th>Normal</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 wks. to 100 days</td>
<td>12</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>22</td>
<td>19</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>101 to 200 days</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>4</td>
<td>14</td>
<td>7</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>201 to 437 days</td>
<td>66.6</td>
<td>33.3</td>
<td>63.3</td>
<td>63.3</td>
<td>86.6</td>
<td>73.3</td>
<td>67.3</td>
<td>73.3</td>
</tr>
<tr>
<td>7 wks. to 437 days</td>
<td>33.3</td>
<td>20.0</td>
<td>66.6</td>
<td>63.3</td>
<td>86.6</td>
<td>73.3</td>
<td>67.3</td>
<td>73.3</td>
</tr>
</tbody>
</table>

**Incidence in Relation to the Primary Lesion.**—No constant relationship was noted between the extent of the primary lesion of vaccination and the incidence of acquired tuberculosis. Some vaccinated rabbits developed fatal tuberculosis in the presence of extensive local primary lesions containing living tubercle bacilli, e.g. I-2, I-3-2, and I-1-7, and other rabbits with slight or no residual primary lesions resisted infection for a long time, e.g. I-1-1, I-1-3, and I-2-6. Nor was there any constant relationship between the incidence of the disease and the interval elapsing between vaccination and exposure; for example, I-3-2 died from generalized tuberculosis after having been exposed, 35 days after vaccination, for 196 days, and Rabbit I-4-0 developed only slight tuberculosis after having been exposed, 114 days after vaccination, for 191 days.
EPIDEMIOLOGY OF TUBERCULOSIS

Portal of Entry and the Acquired Primary Lesion

The route of infection in each of the 22 normal and 18 vaccinated contacts that acquired tuberculosis is given in Table I; the detailed facts upon which these conclusions were based are recorded in the protocols. In 18 of the 40 cases the location of the acquired primary lesion could be determined with certainty. In the remaining 22 cases the diagnosis of a respiratory infection was based upon observation of tuberculosis of the lungs with or without tuberculosis of the tracheobronchial lymph nodes, in the absence of any significant lesions in the intestines, the mesenteric and cervical lymph nodes. When tuberculosis of the intestines was found with or without tuberculosis of the mesenteric lymph nodes, in the absence of significant tuberculosis of

| Table III |
|------------------|-------------------|-------------------|
| **The Portal of Entry in Normal and Vaccinated Rabbits with Tuberculosis Acquired by Contact** |
| | Respiratory only | Respiratory and alimentary | Alimentary only |
| Normal | Vaccinated | Normal | Vaccinated | Normal | Vaccinated |
| No. | Per cent | No. | Per cent | No. | Per cent | No. | Per cent |
| 14 | 63.6 | 8 | 44.4 | 3 | 13.6 | 1 | 5.5 | 5 | 22.7 | 9 | 50.0 |

the tracheobronchial nodes, the diagnosis of an enteric infection was made. If the cervical lymph nodes were extensively affected the infection was considered to be of alimentary origin by way of the pharynx. When lesions were found simultaneously in the tracheobronchial and mesenteric lymph nodes the diagnosis of a combined alimentary and respiratory infection was made.

Table III shows the marked difference in the route of acquired infection in the normal as compared with the vaccinated animals. In the normal animals the respiratory route was involved either alone or together with the alimentary tract in 17 out of the 22 cases, or in 77.2 per cent. In the vaccinated animal the alimentary route of infection was involved alone in 9 out of the 18 cases or in 50 per cent. It is noteworthy that although 19 normal rabbits had free access to alimentary contagion, being exposed in cages without the wire screen...
partition, nevertheless 12, or 63 per cent, acquired a respiratory infection.

In the rabbits in which the seat of the primary acquired lesion could be determined with certainty the distribution was as follows: In 11 of these the lesion was in the lung, 9 showing single, almost completely caseated tubercles, ranging in size from 4 to 12 mm. These were found in all parts of both lungs but most frequently in the lower lobe of the right lung. Each of 2 rabbits had 2 primary lesions in the lungs. These lesions in previously normal rabbits were associated with a marked enlargement and caseation of the tracheobronchial lymph nodes. 1 vaccinated rabbit had a single primary lesion in the lung and another in the ileocecal region, with no involvement of either the tracheobronchial or mesenteric lymph nodes. 5 rabbits had multiple primary lesions in the appendix and ileocecal region. 1 vaccinated rabbit, I-3, showed tuberculosis of the mesenteric nodes without any macroscopic lesions in the intestines. Thus the primary lesion acquired by the respiratory route was usually single in contrast to the multiple primary lesions acquired by the intestinal route.

Extent and Character of the Acquired Disease

A glance at Table I will show that the acquired disease was much more extensive in the previously normal animals than in the vaccinated animals. This appeared not only in the extent of involvement of the most susceptible organ, the lung, in which massive consolidation occurred 9 times in the normal contacts and only once in the vaccinated animals, but also in the dissemination to various other organs. Thus the kidney was affected in 14 and the bone marrow in 4 of the 22 normal contacts that acquired tuberculosis, while the kidney was affected in 7 and the bone marrow in 1 of the 18 vaccinated contacts that acquired tuberculosis.

Usually the acquired primary lesion in the lung was completely caseated in the normal contacts, and less extensively caseated in the vaccinated rabbits. Irrespective of the portal of entry the acquired tuberculosis was chiefly seated in the lung, and it was the extent of the disease in this organ that killed the contacts, whether they were normal or vaccinated, whether they acquired the infection by the alimentary or respiratory tracts. In the normal contacts the disease was characterized by a massive caseous pneumonia, as observed in 9 out of the 11 normal contacts that died with tuberculosis (Fig. 1). In the vaccinated animals the pulmonary lesion was usually a disseminated
discrete tuberculosis (Fig. 2). In only 2 vaccinated contacts, I-1-5 and I-1-8, was there caseous pneumonia. It is noteworthy that both these rabbits had been given the smallest vaccinating dose and that in I-1-5 no lesion was observed under the skin before exposure was begun, nor was any subcutaneous lesion of primary infection found at autopsy.

In normal animals the lymph nodes draining the site of the acquired primary infection, whether in the respiratory or in the alimentary tract, were affected in each of the 22 that developed the disease. In vaccinated animals, on the contrary, these nodes were involved in only 6 out of 18 rabbits. It is noteworthy that in only 1 of the 8 vaccinated animals that acquired a respiratory infection were the tracheobronchial lymph nodes affected; namely, in I-1-5 cited above, which behaved in other respects also like a previously normal animal. In 5 out of the 9 instances of contact tuberculosis acquired by vaccinated rabbits by the enteric route the mesenteric lymph nodes were tuberculous. This is to be correlated with the observation that the acquired primary lesion in the lung is usually single whereas the primary lesion in the intestines is usually multiple.

It has been noted that the intestines were more frequently the portal of entry in the vaccinated than in the normal contacts. In accord with this is the observation that the ileocecal region and the appendix in vaccinated rabbits were more frequently diseased than in the normal contacts. In normal contacts significant tuberculosis of the intestines and mesenteric lymph nodes was rarely found in the presence of tuberculosis of the lung and tracheobronchial lymph nodes, although miliary tubercles were sometimes found in the intestines in association with a generally disseminated disease.

The route of infection influenced the course of the disease. This is clearly seen in the normal contacts that survived exposure for the longest period, such as N-2-2, N-1-9, and N-1-8. The extent of the disease acquired by the enteric route in these rabbits was much less after an exposure of 354 to 375 days than was the extent of tuberculosis of respiratory origin in similar contacts that died after an exposure as short as 122 days. In man, too, tuberculosis of alimentary origin is definitely more chronic in nature than the respiratory disease (5).

A lesion that is rarely seen in rabbits artificially inoculated with
bovine type tubercle bacilli was found in the majority of contacts both normal and vaccinated. This is a tuberculosis of the pleura, which frequently simulates very closely the perisucht of cattle, forming nodules, or pearls, which are often extensively caseated and often suspended by pedicles from the parietal or visceral pleura. When pleural involvement does occur in inoculated rabbits, it is seen only after a long continued chronic disease. In rabbits acquiring the disease by contact this lesion occurs soon after the primary lesion is established, whether in the lung or in the intestinal tract. The affection of the pleura may at times be extensive, compressing the lungs in the thoracic cavity. A further distinction of the natural from the artificial disease is the absence of acquired tuberculosis in the liver and spleen, organs that are frequently affected after artificial inoculation. In only 1 of the 40 contacts that acquired tuberculosis, N-2-2, were there a few tubercles in the spleen.

Microscopically the lesion in the lung of previously normal animals is characterized by widespread diffuse pneumatic and interstitial accumulations of large mononuclear and young epithelioid cells. These soon undergo massive caseation, leaving a few intact mature epithelioid cells. Bacilli are found in tremendous numbers during the earlier stages of the process. Mononuclears continue to accumulate about the advancing part of the lesion, and mitosis of these cells is unabated. The unhindered extension of the caseous process leads to hemorrhage and ulceration into the bronchi, resulting in rapid spread of the lesion to uninvolved areas of the lung. Discrete, mature, epithelioid cell tubercles are rare. There is little or no accumulation of lymphocytes about the tuberculous foci, and fibrous tissue formation is abortive, soon succumbing to the advancing caseous process. Vast areas of caseous tissue result, in which the outlines of the original alveolar walls indicate the essentially pneumatic origin of the caseous process.

In vaccinated animals discrete tubercles are formed, characterized by abundant intact epithelioid and giant cells. Tubercle bacilli are found in very small numbers. Caseation is much less extensive. Lymphocytes accumulate about the tubercles, and there is pronounced formation of granulation tissue. Many of the tubercles are resolving. However, despite this definitely healing process, characteristic of reinfection (6), the older caseous foci undergo softening, and tremendous numbers of tubercle bacilli accumulate in these areas, whence they invade the circulation and cause the slow extension of the disease, chiefly in the lung, kidney, and pleura.

Mortality

Out of the 30 normal contacts 11 died of tuberculosis after an average duration of exposure of 198 days, with a range of from 122 to 317
days. Out of 30 vaccinated contacts, 7 died of tuberculosis after an average exposure of 286 days, with a range of from 195 to 375 days. Vaccinated rabbits with fatal tuberculosis survived 88 days, or nearly 3 months, longer than the non-vaccinated contacts that died with the disease. The mortality from tuberculosis in the vaccinated contacts was therefore 13.3 per cent less than among the normal contacts. Thus the difference between the two groups in mortality is of the same magnitude as in the incidence of the disease.

**DISCUSSION**

Experiments are described in which 73 per cent of 30 normal rabbits exposed for about 1 year to cage mates infected with the bovine type tubercle bacillus acquired either a respiratory or an alimentary infection, which was fatal in 50 per cent of the cases. The effect upon contact tuberculosis of a localized non-progressive infection previously induced by vaccination with living tubercle bacilli of the human type, was studied in 30 rabbits exposed under identical conditions at the same time and in the same cages with the normal animals. In the large majority of instances the human type bacilli persisted with their characteristic virulence at the site of inoculation throughout the period of exposure. It was found that vaccination reduced the incidence and the mortality of the exogenously acquired tuberculosis, affected the route of infection, changed the extent and pathological character of the disease, and retarded its progress.

It was noted that the incidence in normal animals increased with increasing length of exposure during the first 200 days, and that further exposure did not increase the incidence of the disease among them. Essentially the same observation was made in a previous study of air-borne infection in guinea pigs, in which the incidence of acquired tuberculosis increased with the duration of exposure up to 2 years, but did not increase beyond that period (2). This may be attributed to factors in natural resistance (7). On the other hand although it is evident that the vaccinated animals were protected during the first 200 days of exposure, for only 36.8 per cent of them developed tuberculosis as compared with 63.3 per cent of the normal animals, further exposure markedly increased the incidence of the disease in this group.

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4 Lurie (2), 1930, page 743.
This might be thought of as due to the retarding effect of vaccination. However, the incidence of tuberculosis among the vaccinated animals exposed for from 201 to 437 days was actually greater than among the normal animals similarly exposed. 8 normal and 8 vaccinated rabbits survived this period, but of these, 4 normal rabbits completely escaped infection after an exposure of from 300 to 432 days, whereas only 1 vaccinated rabbit escaped infection after exposure of similar duration.

In this connection it is noteworthy that one or more fatal cases of contact tuberculosis occurred in each of the 8 cages except one. This was the only cage in which the normal animals escaped infection. However 2 vaccinated rabbits in this cage acquired a slight disease, although they were exposed for a shorter period than the normal contacts. There is no reason to suppose that natural resistance, which saved the normal rabbits from infection, should not also have been operative in the vaccinated animals, especially since there is ample evidence that vaccination gave considerable added protection. It is unprofitable to speculate as to the cause of this apparently deleterious effect that the vaccination seemed to exert on some contacts. This observation must first be confirmed and then studied further.

Although many present day investigators consider adult type pulmonary tuberculosis as usually due to exogenous reinfection, and although in this country work at The Phipps Institute (8) has produced important clinical evidence for this view, there are still eminent pathologists, such as Huebschmann (9) and Selter (10), who with von Behring, Römer, and Ranke consider exogenous reinfection of secondary importance as compared with endogenous metastatic tuberculosis. They base their view on the fundamental experiments of Römer (11) showing that guinea pigs that harbor a tuberculous infection are completely protected against small doses of tubercle bacilli introduced from without. Since the work of Chaussé (12), recently confirmed by Lange (13), showed that only minimal doses of bacilli can come into play in natural contagion, it is maintained that the primary lesion of childhood protects adults against the small numbers of bacilli that may penetrate into the tissues by way of exogenous infection. Furthermore, in a small number of experiments on guinea pigs, Römer found that the tuberculous animals resisted contact infection (14).

It has been noted that the primary lesion produced by vaccination had the essential characters of the primary focus of childhood, and in the majority of cases contained bacilli that retained their virulence when cultured. These lesions did, in fact, confer considerable pro-
tection against infection. Nevertheless 60 per cent of the vaccinated animals acquired tuberculosis. Their disease was unequivocally shown to be of exogenous origin, for both the human type bacillus of the primary lesion, and the bovine type bacillus of reinfection could be isolated in pure culture from the same rabbit. Experimental proof is thus given that exogenous reinfection, acquired by the respiratory or the alimentary route, occurs in animals harboring a primary lesion. Römer's results with cattle are not conclusive in this respect, because the lesions due to vaccination were ephemeral, and in the large majority of instances they appeared completely healed at autopsy, and the human type tubercle bacilli previously contained in them had disappeared (15).

In applying these observations to adult type tuberculosis of man, it must be pointed out that the experimental animals were undoubtedly exposed to larger quantities of bacilli than are available to human beings under natural conditions. Nevertheless the mode of infection was in general the same; that is, continuous, prolonged, intimate contact with a source or sources of contagion, intensified by crowding. Moreover the disease acquired by these rabbits had many important points of similarity to tuberculous disease in white adults. Both are characterized by the failure of development of tuberculosis of the lymph nodes draining the portal of entry, the rarity of spreading lesions of caseous bronchopneumonia, and the limitation of hematogenous spread. On the other hand, although the disease was chiefly pulmonary, extensive cavity formation did not occur in these rabbits. It is impossible to say with certainty that the primary lesion in the vaccinated rabbits caused by the bacillus of the human type affords them a protection against the bovine type bacillus comparable to that afforded man by lesions acquired in childhood against reinfection with the human type bacillus. However there are rare but authentic instances in man of both the human and bovine type bacillus in the same person (16) and some parallel is presented in recent reports by many observers of bovine type tubercle bacilli isolated from human beings with pulmonary tuberculosis of reinfection, that is, of the adult type (17).

It has been observed in normal animals that the disease acquired by the respiratory route was more quickly fatal than disease acquired by
the alimentary route. It is noteworthy that of the normal animals that survived the longest exposure and therefore had the greater natural resistance, those that finally acquired infection acquired it by way of the intestines. Furthermore it is interesting to find that alimentary infection was more common among the vaccinated animals whereas the respiratory infection was more common among the normal animals.

It is well known that as much as 1000 times the amount of bacilli is required to infect an animal through the alimentary tract as through the air passages. In 7 of the cages bacilli were simultaneously available for entry by both routes, and the quantity of bacilli that reached the intestines was greater than the quantity that penetrated to the alveoli, as is indicated by the following evidence. (1) The primary acquired lesion in the lung was usually single, as in man, but the primary lesion in the intestines was usually multiple. (2) The lymph nodes draining the acquired primary lesion in the lung were involved in only 1 of 8 vaccinated animals, whereas the mesenteric lymph nodes draining the primary lesion in the intestines of vaccinated rabbits were much more frequently involved. Nevertheless, owing to the greater vulnerability of the lung, a large percentage of normal rabbits early acquired a respiratory disease, which, as is well known, tends to inhibit the engrafting of the disease by the alimentary route. Normal rabbits of high natural resistance apparently destroyed the small numbers of bacilli that reached the lung only to succumb later to the cumulative larger dosage of bacilli that were absorbed in the lymph follicles of the appendix and ileocecal region. The same considerations explain the greater incidence of alimentary infection among the vaccinated rabbits.

These experiments emphasize anew the important rôle of native factors in resistance against tuberculosis, recently stressed by Lange (18). 27 per cent of normal rabbits completely escaped disease; 40 per cent of vaccinated animals escaped disease. The increased resistance afforded rabbits by vaccination with living virulent tubercle bacilli of the human type enhanced their natural resistance against undoubtedly large quantities of bacilli, but could save only an additional 13 per cent of them from fatal tuberculosis of exogenous origin, acquired by the natural mode of contagion. A study of the heredi-
tary factors in natural resistance by the method described is now in progress.

SUMMARY

73 per cent of normal rabbits exposed for about 1 year to cage mates infected with tubercle bacilli of bovine type acquired a respiratory or alimentary tuberculosis, which was fatal in 50 per cent of the cases. 63.6 per cent developed tuberculosis during the first 6 months.

Of rabbits vaccinated with tubercle bacilli of human type and exposed in the same cages at the same time only 36.8 per cent acquired tuberculosis during the first 6 months. Later this resistance waned, and by the end of the year altogether 60 per cent had developed tuberculosis, of which 38 per cent succumbed.

The disease in the vaccinated rabbits was shown to be of exogenous origin by the isolation in pure culture from the same rabbit of the human type bacillus from the primary infection, and of the bovine type bacillus from the naturally acquired lesion.

The vaccination reduced the incidence, extent, and mortality of the disease, affected the route of infection, changed its pathological character, and retarded its progress. The disease acquired by vaccinated rabbits shared many characteristics with adult type tuberculosis in man.

It is suggested that this method may be used with relative ease in studying many phases of naturally acquired tuberculosis in small laboratory animals.

REFERENCES


EXPLANATION OF PLATE 16

Fig. 1. The organs of normal Rabbit N-4-2, which died after 125 days of exposure in Cage 6 of massive caseous pneumonia. Note the extent of the disease in the kidney. The route of infection was both respiratory and alimentary.

Fig. 2. The organs of vaccinated Rabbit I-2, which died after 240 days of exposure in the same cage. The encapsulated subcutaneous lesion of vaccination with virulent human type tubercle bacilli is depicted in the upper right hand corner. The ulcer in the ileocecal junction is shown between the liver and kidney, in which there is a slight tuberculous lesion. Tuberculous nodules are shown in the mediastinum. The route of infection was enteric.