EFFECTS OF CORTISONE ON EXPERIMENTAL MURINE TYPHUS

I. SUSCEPTIBILITY OF THE SYRIAN HAMSTER TO MURINE TYPHUS AND THE EFFECT OF CORTISONE

CARRIE E. WHITMIRE

Department of Bacteriology, University of Kansas, Lawrence, Kansas

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Investigators who study rickettsial diseases are interested in finding an animal highly susceptible to these diseases. The lack of such an animal has prompted the investigation of numerous animals and the use of various techniques to increase their susceptibility. This is well demonstrated in the literature concerning murine and epidemic typhus. Although the guinea pig, cotton rat, and mouse are in common use in the study of typhus, fatal infections are produced with regularity only when massive doses of viable rickettsiae are injected.

In reviewing the literature on animals which have been tested for susceptibility to typhus infection, no references were found regarding the use of the hamster, although this animal has been used in the study of several infectious agents. Lennette (1941) found hamsters susceptible to the viruses of St. Louis and Japanese B encephalitis by cerebral inoculation. Griffith (1939) found the golden hamster susceptible to bovine, human, and avian tubere bacilli and vole bacilli. Kilham and Overman (1953) showed that suckling hamsters could be used for primary isolation of mumps virus and for serum neutralization tests. Schwartzman and Aronson (1953) have found the cortisone treated hamster useful in studies on poliomyelitis.

It is shown in this report that the hamster is only slightly susceptible to murine typhus and that cortisone treatment greatly increases the susceptibility of the animals.

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Present address: Department of Microbiology, Ortho Research Foundation, Raritan, New Jersey.

MATERIALS AND METHODS

The materials and methods used in this and the two following papers are given below (Whitmire and Downs 1957; Downs and Whitmire 1957). Details pertaining to the separate experiments are given in the body of the papers.

Animals. White mice, unselected for sex, 15 to 17 g, were obtained from Maple Grove Rabbity, Springfield, Missouri. Young immature male hamsters, 4 weeks old, were obtained from John C. Landis, Hagerstown, Maryland. Adult male hamsters, 65 to 110 g, and male guinea pigs, 350 to 450 g, were obtained from Tumblebrook Farms, Brant Lake, New York. Suckling hamsters were reared in the laboratory.

Infectious material. The Wilmington strain of flea-borne typhus, Rickettsia typhi, was used as the inoculum. Approximately 24 yolk sacs were thawed rapidly under tepid running water, diluted with an equal volume of cold sterile 0.5 per cent skim milk and ground for 10 to 15 sec in a sterile cold Waring Blender. Four ml aliquots were shell frozen and stored in the dry ice chest at −50 C. For animal studies, this material was thawed, diluted to 10 per cent with cold sterile skim milk and twofold dilutions were prepared. Immediately prior to the testing of infectious material in animals, a toxicity titration in white mice was performed (Bengston et al., 1944).

Cortisone. Merck, Sharp and Dohme brand “Cortone,” 25 mg cortisone acetate per ml, was used. The appropriate number of mg of cortisone was regulated by the quantity of cortisone injected, 0.1 ml containing 2.5 mg cortisone. When smaller doses of cortisone were desired, it was necessary to dilute the cortisone with sterile saline to obtain the proper quantity. The cortisone was injected subcutaneously in the nape of the neck of mice, cotton rats, and hamsters. Guinea pigs were injected subcuta-
neously in the hind leg. Rabbits were injected intramuscularly in the hind leg.

Preparation of immunizing antigens for mice and rabbits. A modification of the Pults ether extracted rickettsial antigen was used (Craigie, 1945). To remove the yolk sac material which remained after ether extraction and washing in buffered saline the rickettsiae were treated with antioyk sac serum as described by Karp (1954). After the last centrifugation, the rickettsiae were resuspended in sterile saline and made up to a standard suspension giving a turbidity reading of 20 in the Coleman spectrophotometer at a wave length of 600 and 1:10,000 merthiolate was added. The antigen was stored at 5°C until used. The sonic treated antigen used in immunization of rabbits was the Karp treated rickettsial antigen which had been disintegrated by treatment in the sonic vibrator for 60 min.

Complement fixation test. The complement fixing antigen was prepared and the complement fixation test employed according to the method described by Downs et al. (1955).

EXPERIMENTAL METHODS

Experiment I. The recovery of murine typhus rickettsiae from immature Syrian hamsters. The intraperitoneal inoculation of 4 week old hamsters with a 1:30 dilution of infected yolk sac material having a mouse toxic LD₅₀ of 1:90 produced no apparent signs of illness and no deaths occurred. To determine if rickettsial multiplication occurred in the tissues, the hamsters were sacrificed in pairs on fourth, sixth, eighth, tenth, and twelfth days. No gross pathology was observed. However, large numbers of rickettsiae were seen in the stained peritoneal fluid of animals sacrificed on the fourth and sixth days. Spleens and livers were ground, diluted to 10 per cent by weight and injected intraperitoneally into guinea pigs and young hamsters. All tissues contained sufficient typhus rickettsiae to produce a scrotal reaction in the guinea pig, although no symptoms were produced by this second passage in the immature hamster. All hamsters and guinea pigs produced homologous antibodies demonstrated by the complement fixation test. It appears from these results that although no symptoms of infection are present in the immature hamster after intraperitoneal injection, the rickettsiae are retained in the tissues and multiply since they can be passaged to the guinea pig and the hamster in sufficient numbers to produce evidence of infection.

Experiment II. The effect of murine typhus infection on the adult hamster. Murine typhus infections in the guinea pig caused swelling and inflammation of the scrotum. To determine if a scrotal reaction could be produced in the Syrian hamster, 2 adult male hamsters and 1 adult male guinea pig were inoculated intraperitoneally with a 1:40 dilution of infected yolk sac material giving a mouse toxic LD₅₀ of 1:50. The scrotal reaction appeared in both the guinea pig and hamster on the third day and persisted for 5 days. The character of the scrotal reaction in the hamster is presented in figure 2, taken on the fourth day at the height of the reaction. The hamsters were obviously ill during the period marked by the scrotal reaction, although no deaths occurred. With the disappearance of the scrotal reaction, all signs of infection disappeared. A second set of animals inoculated with the same material were sacrificed at the height of the scrotal reaction and Giemsa stains of tunica vaginalis smears demonstrated large numbers of rickettsiae.

To compare the sensitivity of the scrotal reaction in the hamster and guinea pig in response to intraperitoneal infection, a series of animals were inoculated with fourfold dilutions of infected yolk sac material having a mouse toxic LD₅₀ of 1:640. Guinea pigs showed a scrotal reaction in all dilutions inoculated (1:62.5 to 1:64,000). Hamsters were less sensitive and scrotal reactions were produced only when a dilution of 1:1000 or less was used.
Experiment III. Susceptibility of suckling hamsters to murine typhus infection. To determine whether suckling hamsters were more susceptible than young immature and adult animals, a group of 10 to 11 day old hamsters was inoculated intraperitoneally with twofold dilutions of infected yolk sac material giving a mouse toxic LD₅₀ of 1:50. A parallel experiment was run in 15 to 17 g white mice. The infective LD₅₀ for the suckling hamsters was 1:320 while the mice gave an infective LD₅₀ of 1:180. The average day of death for both the hamster and the mouse was 4 to 5 days, depending on the dilution of the inoculum received. In repeating this experiment, 2 groups of hamsters were inoculated, the first group being 9 to 10 days old and the second group being 19 to 21 days old. The inoculum gave a mouse toxic LD₅₀ of 1:110 and a mouse infective LD₅₀ of 1:160. The 9 to 10 day old hamsters gave an LD₅₀ of 1:160, while the 19 to 21 day old animals showed no signs of infection and no deaths occurred. It would appear that the resistance of the hamster to intraperitoneal infection with murine typhus is established between the tenth and nineteenth day.

There is a discrepancy in the relationship of the toxic mouse LD₅₀ dose and the mouse infective LD₅₀ dose in these two tests. In the first series of animals tested, the toxic LD₅₀ was 1:50 and the infective LD₅₀ was 1:180. In the second series, the toxic LD₅₀ was 1:110 and the mouse infective LD₅₀ was 1:160. It has been found that usually one toxic LD₅₀ is the equivalent of at least 1 infective LD₅₀ dose in the mouse and at least 10 infective LD₅₀ doses for cortisone treated mice. There is also a variation in the number of mouse toxic LD₅₀ doses required to kill 50 per cent of the suckling hamsters in the two tests, the first requiring 6.4 mouse toxic LD₅₀ doses and the second requiring 1.45 mouse toxic LD₅₀ doses. If, however, one calculates the number of mouse infective LD₅₀ doses, one finds 1.8 for the first series and 2.7 for the second series. From these results, it would appear that there was a loss in toxicity of the infectious material between the time the toxicity titration was run and the infection of animals for the infective titration in the second series tested.

Whitmire and Downs (1954) have demonstrated that the use of cortisone increases the susceptibility of the white mouse to murine typhus infections. To determine if the susceptibility of a very resistant animal, as the hamster, could be altered by the use of cortisone, the following experiments were undertaken.

Experiment IV. The effect of cortisone on the susceptibility of young Syrian hamsters to murine typhus. To compare the susceptibility and effect of cortisone on the hamster with that already demonstrated in the mouse, a parallel experiment was run with treated and untreated mice. Young hamsters, 4 weeks old, were divided into three groups of 20 each. Group A received no cortisone, group B, 5 mg cortisone (Merck, Cortone), and group C, 10 mg cortisone. The cortisone was administered subcutaneously 6 hr prior to the infectious dose. The mice were divided into two groups of 40 each; one group receiving no cortisone, and the second group receiving 5 mg cortisone subcutaneously 6 hr prior to infection. Both mice and hamsters were inoculated intraperitoneally with 0.5 ml of the twofold dilutions of infected yolk sac material giving an LD₅₀ toxic titer of mice 1:225. The hamsters receiving no cortisone survived the inoculation of typhus, whereas those hamsters receiving 5 and 10 mg cortisone showed an LD₅₀ of 105 and 80, respectively. The mice receiving cortisone showed an LD₅₀ of 2560 while those receiving no cortisone gave an LD₅₀ of 225. Although these results demonstrate that a single injection of cortisone does bring about fatal typhus infections, the cortisone treated hamster is not as susceptible as the untreated mouse.

Hamsters surviving on the twenty-fourth day could be used for a parallel experiment, receiving by subcutaneous injection, a tract, that cortisone, 5 mg, 1 week prior to the injection of the material. They were then tested on October 22.
were examined for the carrier state. They were divided into two groups, the first group consisted of 5 animals, the second group of 13 animals. The group of 5 animals was sacrificed. Complement fixation tests on the sera of these animals gave titers of 1:8 and 1:16. Eggs were inoculated with the spleens and mice were inoculated with both spleen and tunica material. The tissues were ground with alundum and made up to 10 per cent by weight with sterile skim milk. This 1:10 dilution of tissue material was used for injecting mice which had been pretreated with 5 mg cortisone. Eggs were inoculated with the spleen tissue via the yolk sac route. As a general rule, the chick embryos did not die but were sacrificed on the eleventh day. Numerous rickettsiae were found in smears made from the yolk sacs. The mice injected with the spleen and tunica material began to die on the third day and continued to die through the seventeenth day. The percentage of mice dying from each of these inocula and the average day of death are shown in table 1. The number of mice which died from these injections varied with the inoculum. The lowest number of deaths occurred in those mice inoculated with spleen tissue from the hamster inoculated with the 1:160 dilution of infected yolk sac and no cortisone. The low percentage of deaths is probably due to the smaller number of rickettsial organisms in this tissue. As shown above, no hamsters died from typhus infection unless treated with cortisone. When the total per cent of deaths are calculated for spleen inocula as compared with tunica inocula the per cent of deaths is 67.5 and 87.5, respectively. It would appear from these findings that the number of rickettsiae present in the tunica was greater than that found in the spleen. The mice dying as a result of spleen and tunica inocula were autopsied and rickettsiae were demonstrated in tissue impression smears.

In the second group of 13 hamsters examined for the carrier state, each one was treated with a single subcutaneous injection of 5 mg cortisone. This was done to determine if a latent infection could be converted from the quiescent stage into an active and possibly fatal infection. On the third day after this cortisone treatment, five of the animals developed scrotal reactions. Only those animals which had received large infectious doses of yolk sac material developed scrotal reactions. At the time of infection, these animals were 4 weeks old and at the time of this second period of observation they were almost 8 weeks old. This age factor is important because when the animals were first infected they were too immature to show the scrotal reaction which developed later under the influence of cortisone. Two deaths occurred in the hamsters receiving 10 mg cortisone at the time of infection, one having received an original inoculum of 1:20 and the other 1:40 dilution of infected yolk sac material. Both of these deaths occurred on the sixth day after the second cortisone treatment. No deaths occurred in the hamsters which had originally received 5 mg cortisone at the time of infection. It appears that a carrier state is induced when the infecting inoculum is large and that 10 mg cortisone contributed to greater multiplication of the rickettsiae during the original infection than did the 5 mg cortisone treatment. This resulted in an increased number of organisms in the tissues at the time of the second cortisone treatment. Why this effect did not result in a higher LD₅₀ in the 10 mg cortisone treated animals than in the 5 mg cortisone treated animals is not known.

On the forty-third day, the remaining hamsters were bled and complement fixation tests were run on the sera. All sera showed complement fixation titers of 1:8 and 1:16.

Experiment V. To determine the effect of multiple

### TABLE 1

**Demonstration of the passage of typhus rickettsiae in hamster tissues 24 days after infection by inoculation of cortisone* treated mice**

<table>
<thead>
<tr>
<th>Source of Hamster Tissue</th>
<th>Tissue Used for Passage</th>
<th>Per Cent of Mice Dead on the 17th Day</th>
<th>Mouse ADD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original dilution infected yolk sac inoculum</td>
<td>Cortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:20</td>
<td>0.0</td>
<td>Spleen 100</td>
<td>13.5</td>
</tr>
<tr>
<td>1:160</td>
<td>0.0</td>
<td>Spleen 40</td>
<td>4.0</td>
</tr>
<tr>
<td>1:160</td>
<td>0.0</td>
<td>Tunica 80</td>
<td>9.8</td>
</tr>
<tr>
<td>1:80</td>
<td>5.0</td>
<td>Spleen 80</td>
<td>11.5</td>
</tr>
<tr>
<td>1:80</td>
<td>5.0</td>
<td>Tunica 80</td>
<td>6.0</td>
</tr>
<tr>
<td>1:40</td>
<td>5.0</td>
<td>Spleen 50</td>
<td>7.0</td>
</tr>
<tr>
<td>1:40</td>
<td>5.0</td>
<td>Tunica 100</td>
<td>8.2</td>
</tr>
<tr>
<td>1:80</td>
<td>10.0</td>
<td>Tunica 90</td>
<td>10.0</td>
</tr>
</tbody>
</table>

* Mice received 5 mg cortisone 4 hr prior to inoculation with hamster tissues. Control mice, receiving 5 mg cortisone but no tissue, showed no ill effects.

† Average day of death.
doses of cortisone on the course of infection in the adult hamster. Two groups of 20 hamsters were infected with twofold dilutions (1:50 and 1:400) of yolk sac material which gave a toxic LD₅₀ of 1:400 in mice. The control group was treated with saline. The cortisone treated group received two injections of 10 mg each, 24 and 48 hr prior to infection, followed by daily injections of 2.5 mg for 7 days making a total of 37.5 mg per animal. No ill effects were noted in a group of 4 animals receiving cortisone treatment in the absence of typhus infection. The course of the infection was followed by daily examination for the presence of a scrotal reaction and the animals were weighed every second day. It was found that cortisone significantly altered the course of the infection. The untreated animals showed an LD₅₀ of 1:70. All infected animals which were treated with cortisone died, thus the LD₅₀ was greater than 1:400. The cortisone treated animals were obviously ill, sluggish, and emaciated. There was a loss of an average of 12 g, about 10 per cent of their body weight, in the typhus infected untreated animals during the first 6 days. After that time, there was a steady gain in weight. The cortisone treated infected hamsters showed a continual weight loss until the time of death with a total weight loss of as much as 40 g or 36 per cent weight loss. Although the infection was intensified by cortisone treatment, the scrotal reactions demonstrated in earlier experiments and present in the untreated hamsters of this experiment were completely inhibited in the treated animals. Smears of the tunica vaginalis made from treated animals dying from infection showed a greater number of rickettsiae than smears made from untreated animals sacrificed at the height of the scrotal reaction. Giemsa stains of spleen and liver impression smears and peritoneal fluid showed rickettsiae in larger numbers than are ordinarily seen from highly infected yolk sac smears.

Experiment VI. A comparative study of varying infective doses on intraperitoneal infections in the hamster and the effect of cortisone on such infections. The LD₅₀ was determined with and without cortisone treatment, weight changes were in relation to the infectious dosage and cortisone treatment, and the effect of the initial infective dose on the production of the scrotal reaction was determined. Adult male hamsters were used in this experiment. Half of the animals were treated with 5 mg cortisone 24 hr prior to infection and 1.25 mg cortisone daily for 10 days, total 17.5 mg per animal. Normal control animals receiving cortisone showed no ill effects. Control animals not treated with cortisone received injections of saline. The animals were infected with fourfold dilutions of infected yolk sac material having a mouse toxic LD₅₀ of 1:640.

The hamsters which were infected but received no cortisone showed little sign of illness, except for a few days when the scrotal rection was present. The LD₅₀ of the cortisone treated hamsters was 1:64,000. No deaths occurred in the untreated hamsters. Untreated mice injected with the same material gave an infective LD₅₀ of 1:800. When mice were given a single injection of 2.5 mg cortisone 4 hr prior to infection, the LD₅₀ was 1:82,100.

The scrotal reaction in the hamster is dependent on a large inoculum of rickettsiae. As shown in figure 1, a 1:62.5 dilution of infected yolk sac material gave a 4+ reaction. As the infective dose was decreased, the intensity of the scrotal reaction decreased correspondingly. Cortisone treatment completely inhibited the scrotal reaction, even when the inoculum of rickettsiae was large.

The infected cortisone treated hamsters, in contrast to the untreated infected hamsters, were obviously ill. They became weak and drowsy between the fourth and seventh day, depending on the dilution of infected yolk sac material received. Their fur was ruffled and many of the animals showed conjunctivitis. In the heavily infected animals, their backs became arched on the sixth day of infection. The weight loss showed by these animals was similar to that described in the previous experiment. The animals lost up to 40 per cent of their total body weight before death occurred.

Autopsy of infected cortisone treated hamsters showed a fibrinous exudate in the abdominal cavity matting the organs together. An increased amount of milky peritoneal fluid was present in many of the animals, especially those which were heavily infected. Smears of the fluid revealed numerous rickettsiae as did also impression smears of the spleen and peritoneal scrapings. Tunica smears showed solid sheets of rickettsiae. In heavily infected animals the tunica was filled with hemorrhagic areas. Some animals showed a large amount of hemorrhage in the small intestine below the duodenum. The spleen and liver were
greatly reduced in size and the liver was pale in color.

To determine the appearance of the tunica in infected, but untreated hamsters, one was sacrificed at the height of the scrotal reaction and smears made. Numerous rickettsiae were present, but not to the extent seen in the infected cortisone-treated animals. No hemorrhagic areas were present in the tunica. The abdominal cavity contained an excess of fluid but no fibrinous exudate was apparent.

As further confirmation that the cortisone treated animals were dying from typhus infections, the spleen and liver were removed and used for the preparation of Ascoli antigen (Downs et al., 1955). These antigens were used in the hemagglutination-inhibition test with human convalescent sera. These tissues were found to contain four inhibiting units. No inhibition was found with antigens prepared from uninfected animals.

If the hamster were used for the recovery of typhus rickettsiae from the blood of a suspected case of typhus in man, the best results would be obtained by the use of cortisone treated animals. Although the scrotal reaction is suppressed by cortisone treatment, other signs of illness are present and at the first sign of infection the animals could be sacrificed and examined for the presence of rickettsiae in the tunica, spleen, and peritoneal fluid.

**DISCUSSION**

In the studies on typhus the need for a highly susceptible animal has become evident. To facilitate these studies numerous attempts have been made to find a naturally susceptible animal in which fatal infections could be produced regularly with relatively few rickettsiae. The failure to find such an animal has led to many studies with agents which decrease the resistance of an organism to infection. The search for a more susceptible animal in the present study was concerned with a comparison of the susceptibility of the hamster with that of the white mouse, and the guinea pig. The effect of cortisone on typhus infections in the hamster was also studied.

The susceptibility of the hamster was studied in the suckling, immature, and adult animal. In these three age groups three different reactions were to be found. The 10 day old suckling hamster was sufficiently susceptible to succumb to murine typhus infections, whereas, animals 18 days old were not fatally infected. Kilham and Overman (1953) found that a few days difference in age greatly altered the susceptibility of suckling hamsters to encephalitis caused by mumps virus. Hamsters 8 days of age were susceptible while animals 11 days old were resistant. Although suckling hamsters were shown to be more susceptible to typhus infection than white mice, deaths ensued only after the inoculation of a massive dose of rickettsiae.

Studies with the cotton rat have shown that young animals are more susceptible than adult animals to typhus infection (Anderson, 1944). It was for this reason that immature hamsters were studied for their susceptibility. As shown in the results presented here these animals show no signs of infection in the absence of cortisone treatment. The immaturity of the animals prevented the production of the scrotal reaction which develops in the adult animal.

In comparing the sensitivity of the scrotal reaction in the hamster and guinea pig, it was found that the reaction occurred at approximately the same time and persisted for the same length of time. It is noted, however, that this reaction is far more sensitive in the guinea pig than in the hamster. The hamster shows more visible signs of illness during this period than the guinea pig. On the other hand, the temperature of the guinea pig can be recorded at regular intervals and can be charted as objective evidence of infection.

In addition to increasing the susceptibility of the hamster to murine typhus infections, it has been shown in experiment IV that cortisone can be used to light up a latent infection. This has been shown previously with several agents in experimental animals and in latent infections in man. Fred et al. (1951) and King et al. (1951) have shown that cortisone treatment may cause the activation of arrested cases of tuberculosis. Thomas (1953) has shown that streptococcal bacteremia in rabbits can be produced by cortisone treatment 3½ months after streptococcal infection. Price (1955) has shown that latent epidemic typhus infections in cynomolgus monkeys can be activated by the injection of cortisone. He also demonstrated that typhus rickettsiae can be recovered from the inguinal lymph nodes from healthy patients by tissue culture and by the injection of cotton rats. These patients had shown no symptoms of typhus infections for the past 6 years. From the results
of typhus infections in the hamster presented here, and the results of other workers with other agents, it would appear that as long as the body retains the infectious agents in the tissues, the administration of cortisone in large amounts may transform a latent infection into an active infection. In experiment IV, it was shown that under the influence of cortisone a scrotal reaction could be produced 24 days after the original infection. It is noted in experiment VI that continuous treatment of infected hampers with cortisone caused the complete inhibition of the scrotal reaction. This does not occur when the cortisone is restricted to a single injection. It is also noted in this experiment that large numbers of rickettsiae are required for the production of the scrotal reaction. It would appear, therefore, that a sufficiently large number of rickettsiae were present to produce the scrotal reaction 3 days after the cortisone treatment, although the cortisone treatment was given 24 days after the original inoculation, thus an activation of an old infection must have occurred.

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SUMMARY

Ten day old hampers are susceptible to intraperitoneal infection with murine typhus. After the eighteenth day, resistance has been established and the hamster no longer succumbs to infections with murine typhus.

Although no apparent signs of infection are present in four week old hampers, typhus rickettsiae have been shown to be retained in the tissues and to multiply. The rickettsiae can be recovered twenty-four days after infection.

The adult male hamster response to typhus infection is evidenced by the production of a scrotal reaction. Large numbers of rickettsiae are required, however, for production of this reaction.

Cortisone treatment can transform a latent quiescent infection into an active, fatal infection twenty-four days after initial infection in the hamster.

Cortisone treatment greatly increases the susceptibility of the Syrian hamster to murine typhus infection. Continued cortisone treatment suppresses the scrotal reaction, but brings about a fatal infection.

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