BACTERIOLOGICAL OBSERVATIONS ON EXPERIMENTAL BRUCELLOSIS IN DOGS AND SWINE*

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From the time of the earliest investigation of brucellosis it has been recognized that the host-parasite relationship in this disease presents a peculiar and puzzling problem. As the human disease has become better known the problems have multiplied, and it has become desirable to attempt a solution of them through investigations of the disease in the experimental animal. Furthermore, it has been suggested by recently reported studies [1-3] that brucella may be recovered from a considerable proportion of the cases of Hodgkin's disease, and, at the same time, it has been observed that there are striking similarities between human brucellosis and Hodgkin's disease.[1, 4] The latter observations emphasize more than ever the need for more precise information concerning the relation between brucella and its hosts since only through such information can one expect to form an intelligent judgment of the significance of the data in those instances of a co-existence of brucellosis and Hodgkin's disease. In the latter connection, and also in studying the usual form of human brucellosis, one is faced with certain serious difficulties; the more immediately important of these may be stated briefly as follows: (1) As yet there appears to be no absolutely reliable method for the isolation of brucella from the tissues. (2) In cases of brucellosis proved by the recovery of brucella from the blood, the bacteremia appears to be intermittent, the time between its repeated occurrence being extremely variable; this condition is impossible to understand until the reservoir of the organisms responsible for these recurrences of the bacteremia is known with certainty. (3) The precise relation of the cells of the natural host to the organisms that may be obtained from the tissues by culture is not fully understood. (4) The factors which determine the prolonged course and the recurrence of attacks in chronic brucellosis have not been determined. (5) The influence of the host tissues upon the pathogenicity of organisms which remain in the tissues for long periods is only approximately known. (6) The specific mechanisms through which brucella provokes the different defense mechanisms of the host are little understood.

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During the past 2 years we have carried out a series of studies of experimentally induced brucellosis in a variety of animals in an attempt to solve some of these problems. A preliminary report of the general pathological findings in these studies as they relate to the dog and the hog may be found in the Proceedings of the American Association of Pathologists and Bacteriologists.[5] The report which is to follow covers the bacteriological and immunological observations that were made on this same group of animals. In our experiments on the hog, a natural host, and the dog, an unusual host, our chief object was to learn, first, how long the organisms remain in the tissue when they are no longer demonstrable in the peripheral blood, and, second, under such circumstances, in what tissues they may be found most frequently.

Instances of proved spontaneous brucellosis in the dog are few. Kennedy and Eyre[6] obtained four positive agglutination tests for *Brucella melitensis* in 162 dogs tested in Malta. The bacterium was isolated from the tissues of one of these dogs at autopsy. Plantz and Huddleson[7] reported the isolation of *Brucella suis* in pure culture from a testicular abscess in a 3½-year-old dog with a blood serum agglutinating titer of 1:500 by rapid test. Van der Hoeden[8] isolated brucella from the blood of a dog with high agglutinating titer by inoculating a guinea-pig with the blood. Two other dogs with high blood serum titers yielded negative blood cultures. The organism could not be recovered from the liver or the kidney of any of the 3 animals either by direct culture or by guinea-pig inoculation. Reports of the occurrence in dogs of specific agglutinins for brucella have been made by various investigators. This is reviewed by van der Hoeden,[8] Caliri[9] and Feldman, Mann and Olson.[10] In van der Hoeden's[8] review are reported the results of his own experiments in which 11 dogs were infected *per os* with various strains of brucella. Agglutinating and complement-fixing antibodies were regularly found in these animals from 6 days to 3 months following introduction of the organisms. At autopsy, brucella was recovered from 7 animals, the spleen, liver, bone marrow and mesenteric lymph nodes yielding the higher percentages of positive cultures (54.5 to 57.1 per cent). The organism was recovered less frequently from the blood and rarely from the kidneys, bile, or testis. One dog receiving heat-killed brucella *per os* failed to develop demonstrable serum antibodies during the 35 days it was observed. In a later investigation, van der Hoeden[11] reported a group of experiments in dogs in which infection had been produced *per os*, percutaneously by way of the conjunctiva, and by contact with dogs previously infected *per os*. These animals were killed from 1 to

135 days following infection. Brucella was recovered more frequently from the spleen, liver, bone marrow and regional lymph nodes (47.6 to 65.2 per cent), less frequently from the blood (22 per cent) and rarely from kidneys and testis. Van der Hoeden called attention to the most frequent involvement of parts of the reticulo-endothelial system. Feldman, Bollman and Olson [12] recovered brucella at autopsy from 2 of 5 dogs infected intravenously. One of these animals had positive blood and urine cultures when sacrificed on the 39th day. The other did not yield positive cultures during life; at autopsy, 185 days after the inoculation, the organism was recovered from a mesenteric lymph node. Of 6 dogs infected *per os*, 3 yielded positive blood cultures on the 14th day, but no positive cultures were obtained at autopsy. On the basis of these observations Feldman, Bollman and Olson expressed the opinion that spontaneous brucellosis in dogs is rare, since this animal apparently possesses a highly efficient mechanism for protection against *Brucella abortus*.

Both spontaneous and experimental infections with brucella in swine have received considerable attention in recent years. Good and Smith [13] isolated brucella from the fetuses of an aborting cow and inoculated this organism into two pregnant sows intravenously and *per os*. The sows aborted 17 and 19 days, respectively, after infection, and from the fetuses of each brucella was recovered. Weeter [14] reviewed the literature dealing with the early investigations of spontaneous infection of swine and contributed further observations on spontaneous and experimental infection of swine with brucella. In Weeter's observations on spontaneous infection, the organism was isolated three times from 259 nongravid uteri of swine and once from 289 gravid uteri. His attempts to infect adult swine *per os* resulted in the production of agglutinating antibodies in the serum of the animals, but the initial infection and subsequently ingested organisms soon were eliminated completely as indicated by failure to recover the organisms. Young animals showed a high resistance to oral infection by Weeter's cultures. Cotton and Buck [15] found that boars and pregnant sows could be infected regularly with *Brucella abortus* (*suis*) through the conjunctiva. The organism was recovered by inoculating guinea-pigs with the blood from 12 of 13 animals infected in this way. Five of the animals yielded positive blood cultures as long as 6 to 7 weeks following infection; positive blood cultures on the other 7 animals were obtained not longer than 2 to 4 weeks following infection. Brucella was recovered from the liver of 1 sow killed 102 days after infection. The organism was not recovered at autopsy from another sow killed after 102 days, nor from a sow that

died 48 days following infection. Feldman and Olson [16] isolated brucella from 11 of 24 swine with spondylitis. These animals apparently were symptomless and showed no lesions in other parts of the body than the spine. Feldman and Olson [17] also isolated brucella by guinea-pig inoculation from 2 of 102 apparently normal swine. The organisms were recovered from the lymph nodes on the head and in the anterior cervical region; they were also obtained from an abscess of the spermatic cord of one of the animals and from the spleen of the other animal. Gilman, Milks and Birch [18] passed bovine strains of brucella through a series of hogs in experiments which demonstrated the failure of such animal passage to cause bovine strains to assume the characteristics of the porcine type. In the course of these investigations, large doses of organisms were administered intravenously to 18 sows. Brucella was not recovered by guinea-pig inoculation from 2 of the animals, killed at the end of 103 and 59 days respectively. The remaining 16 sows were killed from 21 to 57 days following infection. Brucella was recovered from the lymph nodes of all 16 animals, from the spleen in 4, from the liver in 1, from the ovaries and uterine wall in 4, and from the mammary gland in 4; in no instance was the organism recovered from the blood. Feldman and Olson [19] introduced *Brucella suis* into swine by way of the conjunctiva, intravenously, orally and subcutaneously, and sacrificed the animals 319 days following infection. They found no lesions in these animals and failed to recover the organism by guinea-pig inoculation. From this experiment these workers concluded that swine apparently possess considerable natural resistance to experimental infection with one strain of brucella of porcine origin.

The experience of previous investigators of brucellosis in the dog and the hog thus indicates (1) that both the dog and the hog appear to possess considerable natural resistance to experimental infection with brucella, (2) that positive agglutination tests are not necessarily indicative of infection that can be demonstrated by recovery of brucella from the animal, and (3) that when the organisms are recovered, they are most frequently found in "integral parts of the reticulo-endothelial system" (van der Hoeden [11]).

Materials and Methods

In the present study, our procedures and observations were as follows:

Two strains of *Brucella suis* were selected for inoculation into the test animals: Strain A was isolated from the spleen of a naturally infected hog and was highly virulent for guinea-pigs, regularly producing

gross lesions and often death within 3 to 4 weeks after intraperitoneal inoculation. Strain B was obtained originally at autopsy from a case of Hodgkin's disease; at the time of these experiments, its virulence for guinea-pigs was slight.

Repeated inoculations of the test animals were made at intervals of from 7 to 21 days. In each instance, a freshly prepared bacterial saline suspension from a 48-hour agar slant culture standardized by means of the photronreflectometer was used.

Blood samples were cultured in Bacto-tryptose* broth with subculture to Bacto-tryptose sheep blood agar slants. Tissues obtained at autopsy were ground with sterile alundum and physiological saline solution to produce suspensions; small portions of these were streaked on Bacto-tryptose sheep blood agar plates, the remainder being added to poured plates of the same medium. The tissues selected for culture are noted in Tables I and II. In every instance, lymph nodes from at least two different sites were studied.

EXPERIMENTS

Dogs

Six male and 3 female adult mongrels were selected. Each appeared to be in good condition and weighed about 10 Kg. Preliminary brucella agglutination tests were negative, and brucella opsonocytophagic readings were within normal limits. Each animal was given an inoculum of 10 billion organisms at each injection. Four animals received repeated doses of *Br. suis* (strain B) intravenously; 1 animal, *Br. suis* (strain A) intravenously; 3 animals, *Br. suis* (strain B) intraperitoneally; and 1 animal, *Br. suis* (strain A) intraperitoneally. The dogs receiving *Br. suis* (strain B) were inoculated every 7 days for 105 days (except when it seemed doubtful that the animal would survive an inoculation), and every 21 days thereafter. The 2 dogs receiving *Br. suis* (strain A) were inoculated at 1, 14 and 34 days. The duration of the experiment for each animal is recorded in Table I. All dogs were bled from the jugular vein at frequent intervals for blood culture, brucella agglutination and opsonocytophagic tests.

The bacteriological findings are summarized in Table I and, together with the immunological data, are discussed later.

Swine

Six male and 2 female hogs, 6 weeks of age, were selected from a single litter. Preliminary brucella agglutination tests and blood cultures of both test animals and parent sow were negative. Preliminary

* Product of Difco Laboratories, Inc., Detroit, Mich.

TABLE I

Experimental Data for Dogs, Including Results of Blood and Tissue Cultures

Dog no.	1	4	5	2	10	9	3	6	7
Brucella suis strain received	B	B	B	B	A	A	B	B	B
Inoculations*	21/i.v.	28/i.v.	4/i.v.	35/i.v.	3/i.v.	3/i.p.	39/i.p.	39/i.p.	33/i.p.
Blood cultures†	12/27	23/34	3/5	18/42	3/5	1/5	4/41	0/43	8/34
Duration (in days) of experiment	198	261	38	487	216	186	461	454	308
Fate of animal	Died	Died	Died	Killed	Killed	Killed	Killed	Killed	Killed
Days between last inoculation and death	14	7	8	225	182	152	143	136	132
Days since last positive blood culture	7	7	1	233	101	152	270	None	231
Autopsy cultures:‡									
Spleen	+	+	+	−	−	−	−	−	−
Liver	+	+	o	−	−	−	−	−	−
Kidney	+	+	o	+	−	−	−	−	−
Lymph nodes	+	o	+	+	+	+	−	−	−
Testis	−	+	o	−	o	−	o	−	o
Lung	−	−	o	o	o	o	o	o	−

* Numerator refers to the number of inoculations given, denominator to the route of inoculation. i.v. = intravenous; i.p. = intraperitoneal.

† Numerator refers to the number of positive blood cultures obtained, denominator to the total number of blood cultures done.

‡ o = not cultured; + = positive for brucella; — = negative for brucella.

opsonocytophagic indices of the test group ranged from 2.5 to 8.5. During the experiments all animals were bled at frequent intervals from the tail, the femoral vein, or the jugular vein for blood cultures, brucella agglutination and opsonocytophagic tests.

At intervals of from 4 to 8 days for 98 days, hogs 1 to 6 were inoculated intraperitoneally with *Br. suis* (strain B) in doses started at 70 million and increased by small amounts to 30 billion organisms. Beginning with the 15th week of the experiment, intravenous inoculations of 30 billion organisms were administered to hogs 1 to 5 every 7 to 14 days for the next 112 days, every 21 to 35 days thereafter. By means of a rubber catheter fitted with a syringe, hog 7 was given orally 7 doses of 30 billion *Br. suis* (strain A) organisms at 1, 6, 27, 42, 48, 70 and 111 days. Hog 8 received the same doses intravenously with omission of the 42nd day.

The bacteriological findings are summarized in Table II.

Discussion

Nine dogs were subjected to large and repeated inoculations of *Br. suis*, 5 animals receiving the organisms intravenously and 4 intraperitoneally. The 5 dogs receiving *Br. suis* intravenously showed a high percentage of positive blood cultures when tested from 6 to 14 days following an inoculation; blood samples taken after 14 days yielded no growth, except in one instance (dog 10). Three of the 4 dogs receiving *Br. suis* intraperitoneally occasionally had positive blood cultures, 20 days being the longest observed period between inoculation of organisms and recovery of brucella from the blood. The greater incidence of positive blood cultures in the intravenous group is striking (Table 1): 42.9 per cent (18 of 42) to 67.6 per cent (23 of 34) positive, as contrasted to 0 to 23.5 per cent (8 of 34) in the intraperitoneal group.

No such difference was observed in agglutination and opsonocytophagic tests. In all of the dogs, regardless of route of inoculation or strain of *Br. suis* employed, the agglutination titer for *Brucella abortus* (456) rose to 1:10,240 or higher within 7 to 14 days following the first inoculation and remained at that level until termination of the experiment. The opsonocytophagic indices also rose within 7 to 14 days following the first inoculation and tended to remain high throughout the experiment. Wide individual variations were observed from week to week, but these could not be correlated in any way with the course of the infection. Two control animals, each of which was given three intravenous inoculations of 10 billion heat-killed *Brucella suis* (strain B) organisms at 1, 14 and 35 days, showed a similar

TABLE II

Experimental Data for Hogs, Including Results of Blood and Tissue Cultures

Hog no.	2	3	5‖	1	4	8	6	7
Brucella suis strain received	B	B	B	B	B	A	B	A
Inoculations* (i.p. or p.o.)	15/i.p.	14/i.p.	13/i.p.	15/i.p.	14/i.p.	—	14/i.p.	7/p.o.
Blood cultures in above period†	0/7	0/7	0/6	0/7	0/7	—	0/5	0/6
Subsequent inoculations (i.v.)*	17/i.v.	17/i.v.	18/i.v.	14/i.v.	18/i.v.	6/i.v.	—	—
Subsequent blood cultures†	9/17	7/17	9/17	12/14	7/17	2/6	—	—
Duration (in days) of experiment	436	411	447	245	424	242	98	240
Fate of animal	Killed	Killed	Killed	Killed	Killed	Killed	Died	Killed
Days between last inoculation and death	117	92	128	10	105	131	7	129
Days since last positive blood culture	180	133	169	0	168	208	None	None
Autopsy cultures:‡								
Spleen	—	—	—	+	—	—	—	—
Liver	—	—	—	+	—	—	—	—
Kidney	—	—	—	—	—	—	0	—
Lymph nodes	—	—	—	+	+	+	—	—
Testis	—	—	—	—	0	+	0	0
Lung	0	0	0	+	0	0	0	0

* Numerator refers to the number of inoculations given, denominator to the route of inoculation. i.p. = intraperitoneal; p.o. = *per os;* i.v. = intravenous.

† Numerator refers to the number of positive blood cultures obtained, denominator to the total number of blood cultures done.

‡ 0 = not cultured; + = positive for brucella; — = negative.

‖ Spleen culture positive for brucella at operation on 87th day of experiment.

rise in brucella agglutination titer and opsonocytophagic index during the 157-day period in which they were followed.

At autopsy brucella was recovered from all of the dogs in the intravenous group and from 1 dog* in the intraperitoneal group. Our chief purpose was to determine, if possible, first, how long the organisms remain in the tissues when they are no longer demonstrable in the peripheral blood, and, second, under such circumstances, in what tissues they are most frequently found. Three dogs (nos. 1, 4 and 5) of the intravenous group died on the 198th, 261st and 38th day respectively. In all three instances, the last inoculation and the last positive blood culture occurred too recently to make the positive autopsy culture significant. Three dogs (nos. 3, 6 and 7) of the intraperitoneal group, killed on the 461st, 454th and 398th day respectively, yielded no positive cultures at autopsy. The remaining 3 dogs, 2 (nos. 2 and 10) of the intravenous group and 1 (no. 9) of the intraperitoneal group, were killed on the 487th, 216th and 186th day respectively, and the organism was recovered from each dog at autopsy. In these three instances, a significantly long period of time had elapsed since the last inoculation of organisms or the last positive blood culture (225, 101 and 152 days respectively). So, in these 3 dogs, the tissues from which the organisms were isolated at autopsy are of interest. Spleen, liver, kidney and lymph nodes were cultured in each instance, as well as testis from 2 of the 3 animals. Brucella was recovered from lymph nodes of all 3 dogs. The only other positive culture was obtained from the kidney of dog 2 (Table 1).

Essentially the same experiment was performed on hogs, using repeated inoculations of *Br. suis*. Of the 8 hogs employed, 1 was inoculated orally, 1 intraperitoneally, 5 intraperitoneally initially and then intravenously, and 1 intravenously. Blood cultures on the intraperitoneal and intraperitoneal-intravenous groups were uniformly negative during the 98-day period of intraperitoneal inoculations. During this time, however, on the 87th day of the experiment, 8 days after the 13th intraperitoneal inoculation of organisms, a culture of the spleen obtained at operation from 1 animal (hog 5) was positive for *Br. suis*; cultures of the liver, the peritoneal cavity, a mesenteric lymph node and the bile, made at the same time from this animal, were negative.

* Dog 9 was the one animal of the intraperitoneal group of 4 to be given *Br. suis* (strain A). This was the only evidence encountered to indicate greater virulence of *Br. suis* (strain A) over *Br. suis* (strain B) for either the dog or the hog, despite the marked difference known to exist between the two strains when inoculated into guinea-pigs. The lack of further evidence was particularly surprising in the experiments on the hog, inasmuch as strain A was isolated from a naturally infected hog and might have been expected to be highly virulent when re-introduced into the natural host.

Blood cultures from the orally inoculated animal (hog 7) were uniformly negative. In the group of 6 hogs subsequently receiving intravenous inoculations, the percentage of positive blood cultures was high (Table II): 33.3 per cent (2 of 6) to 85.7 per cent (12 of 14) as contrasted to none obtained during intraperitoneal or oral inoculation. As in the dogs, all cultures made more than 21 days following an inoculation were negative.

Within 40 to 55 days following the first inoculation, all 8 of the animals except hog 7 possessed agglutination titers for *Brucella abortus* (456) of 1:10,240 or higher. These titers were maintained throughout the experiment with two exceptions: The final readings done on hogs 3 and 5 showed titers of 1:5,120 and 1:2,560 respectively, and hog 7 receiving *Brucella suis* (strain A) orally possessed titers ranging irregularly from 1:320 to 1:5,120 from the 7th day until termination of the experiment. Opsonocytophagic indices of all of the animals were variable and not significantly elevated at any time.

The duration of the experiment for each animal is recorded in Table II. No positive cultures were obtained at autopsy from the 2 animals (hogs 6 and 7) receiving inoculations intraperitoneally and orally respectively. Positive autopsy cultures were obtained from 3 of the 6 intravenously inoculated animals.

As in the dogs, we had few animals which could be used to determine the presence of organisms in tissues when they were no longer demonstrable in the peripheral blood. Hog 1 of the intraperitoneal-intravenous group, killed on the 245th day, had a positive blood culture when sacrificed. Two animals (nos. 4 and 8) yielded positive autopsy cultures when killed on the 424th and 242nd day respectively. Both had received intravenous inoculations, their last inoculations or positive blood cultures occurring 105 and 131 days respectively before death. Spleen, liver, kidney and lymph nodes were cultured in each instance, as well as a testis of hog 8. Both animals (nos. 4 and 8) yielded positive lymph node cultures. In addition, brucella was recovered from the testis of hog 8.

Conclusions

1. Brucella usually disappears from the blood stream of both dog and hog within 1 to 3 weeks after an inoculation of organisms, but it can be recovered from the tissues in some instances from 3 to 7 months later.

2. In the absence of a positive blood culture and of all evidences of clinical infection at the time of autopsy, from inoculated dogs and hogs brucella was recovered most frequently from lymph nodes.

In an equal number of instances, the organism was not recovered from any site.

3. When *Brucella suis* is introduced intravenously into dogs and hogs, infection is frequently established, as shown by repeated recovery of the organism from the blood during life or from the tissues at autopsy; but animals so infected may present no clinical evidence of disease. It is extremely difficult to establish infection (demonstrable by recovery of brucella from the animal) by intraperitoneal inoculation. Infection of one hog by the oral route could not be confirmed by recovery of the organism.

4. The brucella agglutination titers of both dog and hog tend to rise early in the course of experimental inoculation with brucella and to remain high. Furthermore, the agglutination titer apparently is not materially influenced by the route of inoculation or the strain of *Br. suis* employed for inoculation; nor was any difference observed in this connection when heat-killed organisms were used instead of live organisms.

5. The brucella opsonocytophagic indices of both dog and hog were variable and could not be correlated in any way with the course of the experimental infection.

6. No striking difference in virulence between the two strains of *Br. suis* employed for the dog and the hog was observed despite the fact that for the guinea-pig the animal strain A was highly virulent and the human strain B only slightly so.

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