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Experimental and Human Brucellosis

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I. CORTISONE AND ADRENOCORTICOTROPHIC HORMONE (ACTH) IN EXPERIMENTAL AND HUMAN BRUCELLOSIS

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Introduction

Studies with experimentally infected animals and in human beings ill with brucellosis have revealed that the granuloma is a characteristic response of the tissues to Brucella [1, 2, 3, 4]. This type of tissue reaction is found particularly in those organs having an abundance of reticulo-endothelial cells, such as the lymph nodes, liver, spleen and bone marrow. In general, it has been observed experimentally that the grandulomatous type of lesion is most often associated with infections due to Brucella abortus, while suppuration and abscess formation occur more frequently following invasion of the tissues by Brucella suis. Infections caused by Brucella melitensis result in less destruction of the tissues than that due to Br. suis, but the former species causes more severe debility. It has been concluded that the nonsuppurative granulomatous lesion represents a good defense mechanism against Brucella, whereas suppuration and necrosis of tissues indicates a less efficient defence mechanism and invasion by a more virulent species of Brucella.

Although the granuloma is a characteristic feature of the tissue reaction in brucellosis, a more basic biologic phenomenon first emphasized by Smith[5], is that the Brucella localize intracellularly. This intracellular parasitism is of considerable significance with respect to the tendency of the disease to become chronic. There is also evidence that the intracellular organisms are afforded some protection against antibiotics, which have been found to be effective in the treatment of brucellosis[6,7]. Extracellular Brucella organisms are quite susceptible to the lethal action of antibiotics. The thesis was entertained that possibly the host-parasite relationship in brucellosis could be disrupted by cortisone, resulting in the dislodgment of Brucella from their intracellular localization. This would then put the bacterial cells in a position to be disposed of by administered antibiotics. In fact, it has been demonstrated that typhoid fever in another infectious disease where the gram-negative bacilli tend to localize intracellularly to the advantage of the bacterial cell[8]. Human beings with typhoid fever have been treated with cortisone[9,10]. It was observed that prompt clinical improvement occurred in those patients receiving cortisone, although the bacteremia in some instances persisted. The simultaneous administration of cortisone and chloramphenicol appeared to yield more favorable results than those obtained only with chloramphenicol.

Tuberculosis is another disease in which the granulomatous lesions simulate those found in brucellosis. Several investigators have observed the influence of cortisone or adrenocorticotropic hormone (ACTH) upon experimentally induced tuberculosis in mice, rats, guinea pigs and rabbits. Hart and Rees[11] found that cortisone enhanced both acute and chronic tuberculous infections in mice. There was more dissemination of the infection in the cortisone-treated animals, and the individual lesions showed more necrosis and caseation, and contained many more tubercle bacilli than were found in the non-treated control animals. Cortisone has been shown to abolish the protection afforded to mice against tuberculous infection following immunization with heat-killed tubercle bacilli, and administration of the steroid also increased the susceptibility of mice to an attenuated strain of tubercle bacillus[12]. Similar findings in tuberculous guinea pigs were reported by Spain and Molomut[13]. They observed that the lesions of the guinea pigs which received cortisone were more extensive, more widely distributed, and less localized than were those of the control animals. Others[14] have shown that cortisone in-

terfered with the therapeutic effect of streptomycin in tuberculous guinea pigs. In the albino rat, a chronic, granulomatous, noncaseating and nonfatal tuberculous infection was changed by cortisone to a disease which was highly fatal. The tissues showed a dissemination of the lesions without tubercle formation, and many more tubercle bacilli were demonstrated than in the control animals[15]. Lurie and his associates[16] working with his inbred strain of rabbits, which had been made highly susceptible to infections with H37RV tubercle bacilli, found that cortisone increased the number of lesions, but the size of the lesions was reduced. They also noted an increase of necrosis and caseation of the lesions, which contained many more bacteria, but the dissemination of the infection appeared to be retarded. While it is beyond the scope of the present report to review the influence of cortisone or ACTH on human tuberculosis, Freeman, et al[17] have pointed out that ACTH caused a marked amelioration of the symptoms, although there appeared to be a dissemination of the infection. Others[18, 19, 20] have called attention to the appearance of a progressive and severe pulmonary tuberculosis in patients following treatment with ACTH or cortisone. The Committee on Medical Research of the Trudeau Society has warned against the use of these agents in patients with active or latent tuberculosis[21]. Le Maistre and his group[22] observed that both ACTH and cortisone caused prompt symptomatic relief and a repression of the lesions in patients with laryngeal tuberculosis. However, there was an immediate relapse following cessation of therapy.

Experimental studies in animals and in human subjects have been carried out with ACTH and cortisone in other granulomatous diseases. Turner and Hollander [23] reported that in experimental syphilis in the rabbit cortisone caused more destruction of the tissues, and a tremendous increase in the number of spirochetes present in the lesions. At least temporary improvement has occurred in patients with chronic pulmonary granulomatosis due to beryllium following the use of ACTH[24]. Contrary to the general note of pessimism associated with the use of ACTH and cortisone in tuberculosis, several favorable reports have appeared with respect to the results with these agents in sarcoidosis[25, 26, 27, 28]. It is of interest that sarcoidosis is benefited by pregnancy[29].

(I) The Influence of Cortisone on Acute Experimental Brucellosis

The effect of cortisone on experimental acute and chronic brucellosis was studied in mice, guinea pigs and rabbits. Infections were established with a representative strain of Br. abortus, Br. suis and Br. melitensis, all of which had been isolated from human sources. White male mice weighing approximately 20 grams were used. The guinea pigs were all males and averaged 300 grams in weight, while white male rabbits weighing around 2 kilograms were studied. An animal was considered to have had an acute infection when but five to fifteen days had elapsed from the time the bacteria were first introduced. A chronic infection was indicated when a month or more had elapsed. A suspension of cortisone, containing 25 mgs. per cu. mml., was injected intramuscularly in the thighs, alternating sides from day to day. Sterile physiologic saline solution was injected into control animals. Two different dosage schedules were employed in the animals with acute infections. Under the first schedule, contisone was administered for three to five days prior to the establishment of infections, and then for five days to two weeks afterwards. Animals were pretreated with cortisone at the suggestion of Dr. Lewis Thomas, who with Mogabgab[30], had reported that rabbits were more susceptible to infections with group A streptococci when pretreated with cortisone. The second schedule of cortisone therapy was started simultaneously with the infection and treatment carried out for two weeks. In the chronically infected animals, cortisone was administered for five days to two weeks.

At the completion of treatment in each group, all of the animals were sacrificed with chloroform. Forty-eight hours prior to death in the guinea pigs and rabits Brucella antigen (brucellergen) was introduced intradermally on the abdomen and evidence of a skin reaction ascertained at the time of sacrifice. Each guinea pig was given 0.15 ml. of brucellergen and each rabbit 0.1 ml. Blood from the hearts was obtained for cultural purposes and for Brucella agglutination tests. Trypticase-soy broth* was used for blood cultures. The tube-dilution agglutination technique was employed, using Br. abortus antigen, and incubating at 37° C. for 48 hours. The liver, spleen, kidney, lung and testes were observed for gross changes, and then appropriate specimens were selected for bacteriologic study and microscopic examination. A section of each organ, freshly cut with sterile scissors, was touched to the surface of trypticase-soy agar. Colonies of Brucella were identified by their appearance on the plates, staining characteristics with Gram's stain, and the results of a macroscopic slide-agglutination test with anti-Brucella rabbit serum. Sections for histologic examination were prepared by fixing the tissues in 10 per cent formalin, and then staining with hematoxylin and eosin, and also with Giemsa.

Results

A. Influence of cortisone on the tissue of normal animals.

1. Mice. The three schedules of daily doses of cortisone were 0.25, 0.5 and 1.0 mg. per mouse. Each of these doses produced side effects when compared to the control animals receiving saline solution. These effects included decreased physical activity, ruffling of the fur, weight loss, and occasional diarrhea. The tissue changes were similar to those reported by Antopol[31]. The livers of the contisone-treated animals were slightly more enlarged and more friable. Gross evidence of disseminated abscesses were frequently observed in the liver, kidneys, and lungs. The lungs appeared particularly susceptible to these suppurative changes; often 50 per cent or more of the tissue being replaced by large abscesses. Microscopic examination revealed the presence of many small abscesses containing polymorphonuclear cells, whose cytoplasm was filled with bacteria, and in a few instances with mycelial fragments. These suppurative areas could be readily differentiated from the granulomatous reaction caused by Brucella. In addition to these "spontaneous" abscesses, there were occasional areas of coagulation necrosis.

2. Guinea pigs. These animals received 10 mgs. of cortisone daily. No side effects were noted, and the gross and histologic examination of the organs revealed little difference from that of the saline-treated controls. The livers were slightly enlarged and more friable. No abscesses were observed, but occasional areas of coagulation necrosis were noted.

3. Rabbits. Cortisone in a dose of 12.5 mgs. daily caused a marked lipemia, an effect not seen in mice or guinea pigs[32]. The cortisone-treated rabbits had enlarged and friable livers with a glossy appearance. Microscopically, the hepatic cells were swollen and had a clear cytoplasm with the nucleus situated at the periphery. There were occasional areas of coagulation necrosis, which were not associated with cellular reaction.

In all three species of animal treated with cortisone the weight of the spleen was reduced, which had been noted by Germath and his group[33] in the rabbit and by Molomut, et al[34] in the mouse. There was also a reduction in the weights of the adrenals in the three species of animals as a result of treatment with cortisone.

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B. Influence of cortisone in acute brucellosis.

1. Mice

Experiment 1. The purpose of this experiment was to observe the effect of pretreating mice with cortisone prior to infecting them with Brucella. There were three groups, the first and second consisting of 20 mice each, and the third group of 9 mice. The 20 animals in the first group were pretreated with 1 mg. of cortisone daily for five days; the 20 in the second group were pretreated with daily injections of 0.04 ml. of sterile, physiologic saline solution; and the 9 mice in the third group served as cortisone uninfected controls, receiving 1 mg. of cortisone daily. After all 49 mice had been pretreated for five days, the animals in the first two groups were infected by injecting into the tail veins approximately 100 million Br. suis. Treatment was then continued for two weeks, at the end of which time all the surviving animals were sacrificed. This schedule of cortisone therapy proved to be too toxic, since none of the uninfected control animals survived the proposed 19 days of treatment, the mean survival time being 14 days. The mean survival time of the infected group of mice was five days after the establishment of the infection, or a total of 10 days of injections with cortisone. It is of interest that all but two of the infected control animals given daily saline injections survived the full 19 days. Because the animals receiving cortisone died spontaneously, no data concerning blood cultures and Brucella agglutinins are available. As noted in Table IA, Brucella organisms were recovered from approximately the same numbers of livers and spleens of the cortisone-treated animals as from the saline-treated group. Cultures of the same organs of the uninfected cortisone-control animals dying spontaneously revealed a variety of gram-negative coliform organisms. Frequently, similar gram-negative organisms were present as overgrowing contaminants in the organs of infected cortisone-treated animals that died spontaneously.

Post-mortem examination revealed that the spleens of all the cortisone-treated animals were reduced in size. The only gross abnormalities observed were abscesses in the livers, spleens and lungs, which were induced by the cortisone, and which have been already described by others for normal animals receiving cortisone. In the animals infected with Brucella, these organisms were recovered from only the livers and spleens. Microscopic examination of the livers of the saline-treated infected animals revealed small lesions situated either in the central portion of the hepatic lobules or in the portal areas, and the cellular infiltrate consisted of lymphocytes, plasma cells and epithelioid cells, but no giant cells were seen. The individual lesions contained little evidence of necrosis and only rare lesions contained polymorphonuclear leukocytes in the center of them. A mean of 9 lesions was found per 10 low-power fields (100X) with a range of 1 to 42. In the infected mice that had received cortisone there was a striking difference in the number and in the appearance of the lesions. In 13 of the 20, the livers were riddled with small lesions, there being a mean of over 25 lesions in each low power field. These lesions showed much necrosis, and little of the structural detail could be determined. Although in the minority, some lesions did not reveal much necrosis. There were mononuclear cells at the periphery, while the centers of the lesions showed early necrosis and infiltration with polymorphonuclear leukocytes. In the remaining 7 of the 20 cortisone-treated mice, the number of lesions was approximately the same as in those animals receiving saline solution, but the individual lesions showed more central necrosis, and there was a greater infiltration by polymorphonuclear leukocytes. For all the cortisone-treated infected with Brucella, the mean number of lesions in the liver per 10 low power fields was 195.

Preparations of livers with Giemsa stain from the cortisone-treated, in-

fected animals revealed a striking appearance. In the livers with extensive changes, each lesion was teeming with massive numbers of small, gram-negative cocco-bacillary organisms, arranged in clumps, and giving the typical appearance of Brucella. That these organisms were most likely Brucella was proved by recovering Brucella on culturing the liver. In addition, similar bacteria were occasionally seen in the hepatic parenchymal cells adjacent to the necrotic lesions. The cytoplasm of these hepatic cells was packed with organisms. Many Kupfer cells also contained similar bacteria. In the livers from several animals, there were clumps of organisms in the hepatic sinusoids with no apparent cellular reaction around them. In the cortisone-treated mice, whose organs were not so extensively involved, the number of organisms seen in hepatic lesions was much less, and in several animals no bacteria were observed. In the saline-treated infected animals, only rare bacteria were seen, and then with some difficulty. When bacteria were present they were observed in the individual lesions, and none were seen in the parenchymal cells. In the uninfected cortisone-treated controls, bacteria were seen only in the abscesses.

The spleens from the cortisone-treated and the saline-treated infected animals showed little difference histologically. These organs from both groups contained giant cells in moderate numbers but were otherwise not remarkable. Occasional cells in the spleens of the infected cortisone-treated mice contained moderate numbers of bacteria, but the extensive involvement as seen in the livers was not present. No bacteria were observed in the spleens of the saline-treated infected mice.

Experiment 2. Because a daily dose of 1 mg. of cortisone proved to be too toxic for uninfected mice, the preceding experiment was repeated using smaller doses of the steroid in an attempt to keep the mice living until sacrificed, and also, to note the effect of cortisone upon the course of the infection after the injections had been discontinued. An initial group of 18 mice were infected intravenously with Br. suis, and then 13 received daily injections of cortisone, and 5 received saline solution. Four uninfected mice served as cortisone control animals. Treatment with cortisone or saline solution was started three days prior to infection and continued for ten days thereafter. For the first six days all the mice received 0.5 mg. daily, but this dose also proved to be too toxic and so the dose was reduced to 0.25 mg. for the next seven days. Even this latter dose was more toxic than desired since all the animals that had received cortisone died by the twelfth day of therapy. Because the mice were dying spontaneously, five infected animals being treated with cortisone and five being treated with saline solution, were sacrificed on the eleventh day of therapy, or the eighth day of the infection.

A second group of mice were given 0.5 mg. of cortisone for a shorter period of time. Seventeen mice were infected with Br. suis, and 13 received cortisone, while four were given saline solution. Treatment was instituted three days prior to infection. It was planned to continue treatment for seven days thereafter, but only one of the 13 mice receiving cortisone survived this period. Two mice receiving cortisone, and two receiving saline solution, were sacrificed on the sixth day of their infection, or the ninth day of treatment. The original plan of the experiment could not be carried out in the two groups of mice because the animals did not survive long enough.

There were no significant differences in the results in the two groups of animals (Table IB). Cultures of the hearts' blood in all of the sacrificed infected animals showed the presence of Br. suis. The spleens of the cortisone-treated animals were approximately three times smaller than those that had received saline solution. On the other hand, the spleens in the two groups receiving 0.5

mg. cortisone were twice as large as those from the mice that had received 1 mg. of cortisone daily. Abscesses were noted in the organs of the cortisone-treated animals as in the preceding experiment. Brucella organisms were also recovered from the cultures of the livers and spleens of the sacrificed animals, but in those animals dying spontaneously the cultures were overgrown with enteric organisms. It was noted that there were many more colonies of Brucella on the culture plates from the organs of those animals that had received cortisone.

Microscopic examination showed that the livers from the infected animals treated with cortisone had many more lesions than the animals treated with saline solution. In 17 of the cortisone-treated animals there were at least 12 individual hepatic lesions per low-power field (100X). The remaining cortisone-treated animals had less involvement and were similar to the saline-treated group. In this experiment, the hepatic lesions did not reveal the marked necrosis that was present in the mice of the preceding experiment where 1 mg. of cortisone daily was administered. Only three of the cortisone-treated animals showed the extensive involvement of the liver with necrosis that was described for the preceding experiment. However, there was more necrosis, and there were fewer lymphocytic cells in the lesions of the cortisone-treated animals as compared to saline-treated control mice. Specimens of liver prepared with Giemsa's stain showed the presence of bacteria, having the appearance of Brucella, in the majority of lesions in the infected cortisone-treated group. Only three mice showed the presence of massive numbers of Brucella in the liver that was so prevalent in animals that had received 1 mg. of cortisone daily. In two of these animals, an occasional hepatic cell had cytoplasmic parasitization. No bacteria were seen in the livers of the group receiving saline solution.

Experiment 3. Since the administration of cortisone was uniformly associated with a marked diminution in the size of the spleen, this gave rise to speculation concerning the effect of cortisone on the course of brucellosis in splenectomized mice. Fortunately, there were available in the laboratory nine healthy mice that had been splenectomized over a year previously. For five days, five of these mice were given 0.5 mg. of cortisone daily, while four received 0.02 ml. of saline solution. After this "pre-treatment" the animals were infected with Br. suis, as in the preceding experiments, and cortisone or saline solution was administered for only six days and sacrificed, because at this time, one of the cortisone-treated animals died (Table IC). Brucella organisms were recovered from the hearts' blood and organs of all the animals. Cultures of the liver on agar plates revealed more colonies of Brucella from the cortisone-treated mice than from the saline-treated animals. Microscopically, the liver, kidneys and lungs from the splenectomized mice showed much more extensive involvement by Brucella than has been described elsewhere for intact animals[35]. In two of the cortisone-treated mice, the livers were extensively involved, with 25 lesions per low-power field (100X). In the remaining mice, the number of hepatic lesions approximated those present in the saline-treated controls. The microscopic appearance of the hepatic lesions was similar to that described for the preceding experiment. It is of interest that in the saline-treated mice there was much more of a dissemination of the infection to the other organs than was present in the cortisone-treated group. All of the saline-treated animals had lesions in the kidneys and lungs, as well as the livers, while two of the five cortisone-treated animals had demonstrable lesions confined only to the liver. There was no essential difference in the hepatic and extrahepatic lesions. In all the mice the lesions showed a cellular infiltrate consisting of mononuclear cells, plasma cells and lymphocytes, but without polymorphonuclear leukocytes or necrosis.

Sections of the livers, kidneys and lungs prepared with Giemsa's stain showed in four of five cortisone-treated mice the presence of Brucella in the hepatic lesions, and

only in one was there massive numbers of bacterial clumps and a rare parasitization of hepatic parenchymal cells. Only two of the saline-treated group showed organisms in the hepatic lesions, and a very few could be seen. No organisms were demonstrated in the kidneys or lungs of either group.

Experiment 4. In all of the preceding experiments, the animals were pretreated with cortisone before they were infected with Brucella. In the present experiment, treatment with cortisone was started simultaneously with the institution of the infection. As before, 18 mice were infected intravenously with about 100 million organisms of Br. suis. Ten mice were then given 1 mg. of cortisone daily for two weeks, and eight were injected daily with 0.04 ml. of sterile physiologic saline solution for the same period. For uninfected, cortisone-treated control animals, the mice in the preceding experiment were used, since both experiments were carried out concurrently. The mean survival time for the mice receiving cortisone was 12 days, while the saline-treated mice survived the full two week course of therapy. At the end of two weeks of treatment all of the surviving animals were sacrificed. The results are summarized in Table ID. Brucella was recovered from cultures of the liver of four out of 10 cortisone-treated animals and two of the eight saline-treated mice, while the cultures of the spleen yielded Brucella in five of the cortisone-treated mice and in seven of the saline-treated group. It was again noted that more colonies of Brucella appeared on the agar plates from the organs of the cortisone-treated animals, and the colonies appeared more rapidly than those obtained from the saline-treated mice.

Microscopically, it was noted that there was more extensive involvement of the livers from the cortisone group, but not as much as had been observed in the mice which had received cortisone prior to being infected. The necrosis of the liver parenchyma and infiltration with polymorphonuclear leukocytes as seen in the pretreated animals was not present to such a great degree in the present experiment. However, there was definitely more hepatic necrosis in the cortisone group than in the saline-treated controls. No essential differences were noted in the spleens of the two groups. Giemsa stain revealed bacteria in the sections of the liver of all the cortisone-treated mice, but only in moderate numbers, there being an absence of the extensive parasitization seen in the pretreated mice.

2. Guinea pigs

Experiment 5. The purpose of this experiment was to pretreat guinea pigs with cortisone, and then to infect the animals with Brucella. Representative animals were infected with one of the three species of Brucella in an attempt to see if cortisone influenced each of the infections differently. Braude[36] had demonstrated that each of the species of Brucella produced a different reaction in guinea pigs. Three pairs of guinea pigs were used. One animal of each pair received cortisone, and the other received sterile, physiologic saline solutions. Each selected guinea pig received 10 mg. of cortisone daily for five days, and then one animal each was infected intraperitoneally with approximately 1 billion colonies of Br. melitensis, Br. suis and Br. abortus. Injections of cortisone or saline were then continued for five days, and then all the animals were sacrificed. The results are presented in Table IIA. It is of interest that no agglutinins were demonstrated in the bloods of any of the animals, and cultures of the blood remained sterile. However, Brucella organisms were recovered from the livers and spleens. There were more colonies of Brucella recovered from the organs of the cortisone-treated guinea pigs than from those receiving saline. Microscopically, the only significant lesions were in the liver. There was no essential difference noted between the lesions of the cortisone-treated animals and the saline-treated group except in the two animals infected with Br. suis. In the animals

receiving only saline solution the hepatic lesions consisted of small granulomata with lymphocytes, plasma cells and mononuclear cells. Very little evidence of necrosis was present. However, in the cortisone group there were many more lesions present with infiltration by polymorphonuclear leukocytes and more evidence of necrosis. There was no difference in the weights of the spleens in the two groups. Giemsa staining of the liver did not reveal the definite presence of organisms.

Experiment 6. Because Br. suis caused more reaction in the tissues of normal animals than did the other two species of Brucella, further studies were carried out with this species alone. Ten guinea pigs were used, five receiving 10 mg. of cortisone daily, and five were given saline solution. After five days of treatment, each animal was injected intraperitoneally with about one billion organisms. It was planned to continue treatment for two weeks after infecting the animals. One guinea pig died on the fourth day of infection, and another on the eighth day. All the other animals were sacrificed two weeks after institution of the infection. The results are presented in Table IIB. The skin of none of the animals reacted to the intradermal injection of Brucella antigen. Brucella was recovered from the hearts' blood of the three surviving cortisone-treated animals, and from three out of five saline-treated guinea pigs. Agglutinins were present in all the animals, there being no difference between less than the saline-control group. Brucella cells were uniformly recovered from the organs of all the sacrificed animals with the cultures of the cortisone- treated group showing more colonies. Cultures of the organs of those animals that died were overgrown with coliform bacteria.

Microscopic examination of the livers and spleens revealed no difference in the number, size and type of lesions between the two groups of animals. Giemsa stained sections showed no difference in the number of organisms.

3. Rabbits

Experiment 7. The purpose of this experiment was the same as that of Experiment 5. Three rabbits were pretreated with daily injections of 12.5 mg. of cortisone for five days, and three were given saline solution. All six rabbits were then infected intravenously with 1.25 billion organisms. Each cortisone-treated rabbit was paired with a saline-treated control and one pair was given Br. melitensis, another Br. suis, and a third pair Br. abortus. Treatment was continued for five days after initiating the infections and then the animals were sacrificed. The results are summarized in Table IIIA. The intradermal reaction to Brucella antigen was positive in the three saline-treated rabbits, but only slightly positive in one of the cortisone-treated animals and absent in the other two. There was also a significant reduction in the agglutinin titer of the cortisone-treated animals compared to those receiving saline solution. The weights of the spleens was markedly reduced in the cortisone-treated group. Cultures of the organs from all the rabbits yielded Brucella, with more colonies being recovered from the cortisone-treated animals.

Microscopic examination revealed lesions only in the liver. The livers of those animals that had received saline solution showed lesions consisting of small granulomata with lymphocytes, plasma cells and mononuclear cells. There was very little necrosis. The livers of the cortisone-treated animals contained more lesions, and there was more necrosis with infiltration by polymorphonuclear leukocytes, and diminution in the number of lymphocytes and plasma cells. In sections of liver prepared with Giemsa stain bacteria were seen only in those obtained from the cortisone-treated animals. Since cultures of these tissues yielded only Brucella it can be assumed that Brucella were being seen with the aid of Giemsa stain. Brucella organisms were seen only

in the livers of the animals infected with Br. melitensis and Br. suis. The animal that had received Br. melitensis showed hepatic lesions packed with cocco-bacillary organisms, and at the periphery of these lesions there were occasional parenchymal cells whose cytoplasm was filled with organisms. The hepatic lesions of the animal that had received Br. suis contained many bacteria, but none were seen in the hepatic parenchymal cells.

Experiment 8. In this experiment 10 rabbits were selected for study. Five received 12.5 mg. of cortisone daily for five days, and then were infected intravenously with 1.25 billion organisms of Br. suis. Treatment with cortisone was then continued for two weeks. Five control animals were given saline solution instead of cortisone and then infected in the same manner. All surviving animals were sacrificed on the fourteenth day of the infection. One cortisone-treated rabbit expired on the eighth day of the infection, and two were critically ill at the time they were sacrificed. Just prior to death the Brucella skin test was negative in all of the animals. Br. suis was recovered from the blood cultures of all the animals that had survived the infection for two weeks (Table IIB) Agglutinins for Brucella were present in all of the animals, and there was no difference in titer between the cortisone and saline-treated animals. The weights of the spleens in the cortisone-treated animals were considerably reduced compared to the saline-treated controls. Colonies of Br. suis were recovered from the livers and spleens of all the cortisone-treated rabbits, and in greater numbers than were obtained from the saline-treated animals.

Microscopically, the only significant lesions were in the livers. There were approximately the same number in the cortisone-treated rabbits as in the controls, except in the animal that did not survive the two weeks. In this animal there was extensive involvement of the liver with about 70 per cent of the organ occupied by almost completely nectoric lesions. The individual lesions in the four remaining cortisone-treated animals showed slightly more necrosis and infiltration with polymorphonuclear leukocytes than those of the saline-treated group. No renal lesions were seen. Sections prepared with Giemsa stain revealed bacteria only in the rabbit that died before the experiment terminated. In this animal, the hepatic lesions were massively invaded by bacteria.

(II) The Influence of Cortisone on Chronic Experimental Brucellosis

A. Mice

Experiment 9. Twenty-four mice were infected intraperitoneally with Br. suis, each animal receiving 100 million organisms. All the animals survived this infection for one month. At this time, 12 mice were given 1 mg. of cortisone daily and the other 12 were injected with saline solution. It was planned to treat all of the animals for two weeks, at which time all the surviving animals were to be sacrificed. The mean survival time of the cortisone-treated animals was 11 days, while all of the saline-treated controls survived the two weeks. The results are tabulated in Table IVA. It was not possible to compare the results of blood cultures and Brucella agglutinins. The spleens of the cortisone-treated animals were smaller than the saline-treated mice, but larger than the cortisone uninfected controls studied in Experiment 1 (see Table IA).

Microscopic examination of the organs revealed little difference between the cortisone-treated and saline-treated groups. Only occasional lesions were seen in the livers, and in both groups these lesions were similar. There were small granulomata with mononuclear cells, plasma cells and occasional epithelioid cells. There was no increase in the number of polymorphonuclear leukocytes or in necrosis of the individual lesions in the cortisone-treated animals as compared with the mice that had received

saline solution. Giemsa stained sections failed to reveal any organisms in the lesions of any of the animals.

Experiment 10. A group of 22 mice, each of which had been infected with one of the three species of Brucella, had been kept in the laboratory for 10 to 12 months. None of these mice had received any drugs, and they appeared healthy. The composition and treatment of this group was as follows: nine mice infected with Br. melitensis, five of which were given 4 mgm. of cortisone daily, and three were given 0.16 ml. of saline solution; five mice infected with Br. abortus, two of which received cortisone and two were given saline solution in the same doses as above; four mice that had been infected with Br. abortus following splenectomy, two of which received cortisone and two received saline solution; four mice infected with Br. suis, two of which received cortisone and two received saline solution. In addition to these 22 mice, there were two uninfected animals added as controls, which received 4 mg. of cortisone daily. Treatment of all the mice was continued for two weeks, when all the surviving animals were sacrificed.

The results are presented in Table IIIB. The mean survival time of the cortisone-treated infected animals was nine days, while that of the cortisone controls was 11 days. All of the animals receiving saline solution survived the planned period of two weeks of therapy. An attempt was made to obtain blood cultures from each animal during the course of therapy by clipping the tail and allowing one or two drops of blood to fall on an agar plate. With this method, only one positive blood culture was obtained, and this one was a cortisone-treated animal from which Br. abortus was recovered. At the time the animals were sacrificed, an endeavor was made to obtain sufficient blood for the agglutination reaction and for blood cultures. No agglutinins were demonstrated in the bloods of two cortisone-treated animals, while four of nine mice that had received saline solution showed a mean titer of 1 to 320. The heart's blood of one cortisone-treated animal was cultured and no Brucella organisms were recovered, and from the blood of eight saline-treated mice, Brucellae were recovered from one. The mean spleen weight of the infected cortisone-treated group was considerably less than the saline-treated controls, but much greater than that of the uninfected cortisone-treated mice. Cultures of the organs for Brucella were positive in three of the cortisone-treated group, two of the animals having positive cultures from both the livers and spleens, and one from the spleen alone. In the saline-treated group, Brucella was isolated from only the livers of two of the animals. Various coliform organisms were recovered from the organs of the uninfected cortisone-treated controls.

Microscopically, very few hepatic lesions were found in any of the animals, regardless of the type of therapy. When lesions were present, they consisted of small granulomata, composed of mononuclear and epithelioid cells, but without giant cells, necrosis or polymorphonuclear leukocytes. There was no difference in the appearance of the lesions between the cortisone-treated group and those that had received saline solution. Each spleen from the infected animals contained giant cells and a reduced number of germinating follicles, and this varied from animal to animal, but there was no correlation between the appearance of the lesions and the type of therapy. It is of interest that renal lesions consisting of granulomata were seen only in the splenectomized mice that had been infected with Br. abortus, and these lesions were present in both animals that had received saline solution, but not in the two cortisone-treated mice.

B. Guinea pigs

Experiment 11. Three pairs of guinea pigs were infected intraperitoneally with approximately one billion Brucella cells; one pair receiving Br. suis, one pair Br. melitensis, and one pair Br. abortus.

One month after the organisms had been injected, one animal in each pair was treated with 10 mgs. of cortisone daily for 14 days, and the three control animals were given saline solution. Just prior to starting therapy, and at the conclusion of five days of treatment, blood was obtained from each animal by cardiac puncture for cultures and for agglutination tests.

The results of this experiment are summarized in Table V. There was no essential difference in the results of blood cultures obtained before and after treatment with either cortisone or saline solution; nor was there any significant difference in the agglutinin titers. The skin reaction with Brucella antigen was less in the cortisone-treated animals. The weights of the spleens from the animals that had received cortisone were less than the saline-treated controls, but the differences were not so great as observed in the animals having more acute infections and treated with cortisone (see Experiment 5 and 6, Table IIA and IIB). Brucella organisms were recovered from the livers and spleens of two out of the three cortisone-treated animals, and from the organs of all three saline-treated controls. There was no significant difference in the number of bacteria obtained from the organs of the two groups. Microscopic examination of the livers, spleens and kidneys revealed only a few small lesions in the livers, and the type of therapy did not appear to effect the histologic appearance of these hepatic lesions. Giemsa stained preparations did not reveal the presence of any organisms.

C. Rabbits

Experiment 12. This experiment was similar to Experiment 11, which was carried out with guinea pigs. Three pairs of rabbits were infected intravenously with about one and one-half billion Brucella organisms. One pair received Br. melitensis, one pair Br. suis, and one pair Br. abortus. One month was permitted to elapse after the institution of the infection and then three animals were given 12.5 mg. of cortisone daily for 14 days, and three received saline solution. Skin tests were performed just before the animals were sacrificed. The reactions in the cortisone-treated animals showed smaller nodules and less edema than the saline-treated controls. Blood obtained by cardiac puncture just before instituting treatment and at the time of sacrifice did not show any significant difference in the blood cultures and agglutination tests in the two groups of rabbits. (See Table VIA) The average weights of the spleens of the cortisone-treated animals were definitely less than the saline-treated controls. Cultures of the livers and spleens from the animals that had received cortisone did not reveal any Brucella, whereas these organisms were cultured from the livers of two of three saline-treated rabbits and from the spleen of one. A very few hepatic lesions were noted microscopically, but there was no difference in the appearance of the lesions in the cortisone-treated and saline-treated animals. No bacteria were seen in the Giemsa stained organs of either group.

Experiment 13. In the preceding experiment, rabbits had been infected for one month before being treated with cortisone. In the present experiment, rabbits were used that had been infected for four months. These animals had been infected intravenously with Br. abortus in a total dose of 18.75 billion organisms given in five divided doses. Three of the animals were given 12.5 mgs. of cortisone daily for 14 days, and one was given 0.5 ml. of saline solution for the same period. The results are presented in Table VIB. It is of interest that blood obtained by cardiac puncture before and after treatment did not contain any Brucella, while Br. abortus was recovered both times from the one saline-treated control. The mean blood agglutinin titer of the cortisone-treated animals was 1:1280 just before treatment, and 1:160 at the conclusion of treatment. The titer in the one saline control animal was 1:2560 before treatment, falling

to 1:640 after therapy. The mean weight of the spleens in the cortisone-treated animals was much less than that of the saline-treated control. No Brucella organisms were recovered from the livers or spleens of any of the animals, and no lesions were seen microscopically in the livers, spleens and lungs.

Comment

The primary objective in the foregoing experiments was to determine the effect of cortisone upon the host-parasite relationship in experimentally infected animals with acute and chronic brucellosis. The outstanding effect of cortisone was observed in the mouse with acute brucellosis, where a relatively mild and nonlethal infection was converted into a rapidly fatal disease within a few days. The most striking tissue changes observed throughout the entire study, which were induced by cortisone, were found in the liver. Again, these hepatic changes were prominent in the mouse with acute brucellosis. A liver with a moderate number of granulomatous lesions was converted into an organ having a pronounced increase, not only in the number of lesions, but also an increase in the amount of necrosis that was present. Cortisone not only intensified the alteration of tissue containing Brucella, but it also caused a definite increase in the number of Brucella present in the acute lesions of mice, guinea pigs and rabbits, but particularly in the mouse. Of special interest was the intense parasitization of the hepatic parenchymal cells surrounding the lesions. In addition, the Kupfer cells in the livers of the cortisone-treated mice and in one of the rabbits were engorged with massive numbers of Brucella. The influence of cortisone upon acute brucellosis in the mouse, and especially upon the hepatic lesions, was related to the dose of cortisone. When 1 mg. was administered daily, there was more involvement of the liver, more necrosis of the lesions, and a greater number of bacteria present, than in those animals receiving 0.5 mg. or 0.25 mg. daily. Pretreating the animals with cortisone shortly before infecting them with Brucella enhanced the deleterious effect of cortisone on the infection.

In contrast to the effect of cortisone upon acute brucellosis in the mouse, the agent did not appear to effect the course of the disease in the guinea pig, and it provoked only a moderate enhancement of the infection in the rabbit. Hypersensitivity, as measured by the skin reaction with Brucella antigen, was depressed in the guinea pig and rabbit by cortisone. Suppression of skin reactions has been observed in other infections[37, 38, 39]. Cortisone did not appear to cause a consistent change in the titer of Brucella agglutinins.

One of the effects of cortisone that provoked attention was the consistent diminution in the size of the spleen of the cortisone-treated animals. In a previous study in mice by Braude and Spink[40], it was demonstrated that the spleen plays an important role in the defense against Brucella, particularly in the protection of the liver. The hepatic lesions in splenectomized mice with brucellosis were more widespread than in infected control animals with spleens. In the present study with a limited number of animals, cortisone did not appear to enhance the damage to the liver by Brucella compared to splenectomized mice given saline solution.

A result that was not anticipated in these investigations was the failure of cortisone to alter significantly the host-parasite relationship in the chronically infected animal. This was in marked contrast to the deleterious effect that cortisone had in the animal with acute brucellosis. Furthermore, these results were unlike those reported for tuberculosis in mice, in which cortisone altered unfavorably a stable and chronic tuberculosis infection[11]. No definitive statement can be made at this time for the differing effect which cortisone has on experimental acute and chronic brucellosis. It is entirely possible that the chronically infected animal escapes

a spread of the infection because immunity to Brucella has been permitted to develop before cortisone is administered. This immune mechanism keeps the infection localized and the number of organisms is kept down, and then if cortisone does disturb the underlying host-parasite relationship with the liberation of intracellular bacteria, an efficient immune process is on hand to prevent the proliferation of Brucella, and invasion of other cells of the host. There is documented evidence that neither ACTH nor cortisone interfere with the production of pneumococcic antibodies[40, 41]. The present investigation demonstrated that Brucella hypersensitivity is considerably decreased by cortisone, but there was no appreciable reduction in Brucella agglutinins.

(III) Adrenocorticotrophic Hormone (ACTH) in Human Brucellosis

Although the studies on brucellosis in animals were carried out with cortisone, the investigations in human patients were made with ACTH. The latter agent was made readily available at a time when the supply of cortisone was very limited.* It was planned at first to treat only those patients who had had a continuation of symptoms for a long time after their initial attack. The outstanding complaints in these patients were weakness, mental depression, nervousness, and aches and pains. After agglutination tests had been done, and blood obtained for culture, the patients were to be given ACTH, and kept under close observation in the hospital. During the course of treatment and after discontinuation of ACTH, agglutination tests were to be performed and blood cultures were to be kept under observation. In case any patient became febrile, or his condition became worse, ACTH was to be discontinued, and aureomycin was to be administered. In addition, after ACTH had been given for a few days, a skin test with Brucella antigen was to be performed to denote the effect of ACTH on dermal hypersensitivity. These patients usually exhibit marked local and systemic reactions following an intradermal test. A brief summary of each patient's illness and response to ACTH is presented below, and the pertinent data on all the patients is given in Table VII. It is to be noted that Cases 2 and 6 involved individuals with acute brucellosis and a bacteremia due to Br. abortus. These patients did not receive any antibiotic during the course of observation.

Patient 1., ., a 28 white married farmer was first hospitalized on June 12, 1950 because of chills, sweats, nausea and vomiting of two weeks' duration. Because of a duodenal ulcer, he had consumed large amounts of unpasteurized milk. There was no recognized Bang's disease in his herd of cattle, but the disease was present in a herd in an adjacent pasture. Physical examination revealed a temperature of 104° F., lymphadenopathy, hepatomegaly and an enlarged, tender spleen. Brucella agglutinins were present in a titer of 1:1280, and cultures of blood yielded Br. abortus on June 13 and June 15, 1950. On June 14, 1950 treatment with aureomycin was started, and he received 0.5 gram four times daily until June 19, when because of nausea and vomiting, terramycin was substituted for aureomycin. He tolerated the antibiotic therapy for a total of 10 days. During this time, the symptoms subsided, and the spleen diminished in size. Blood cultures as of June 26, 27 and 28, 1950 remained sterile. On June 26, the agglutinin titer was 1:1280. He was discharged from the hospital on June 29, 1950. When seen on July 28, 1950 he was afebrile, and he had no complaints. The spleen was palpable at the costal margin. The titer of agglutinins was 1:320, and a blood culture was sterile. When observed from February 8 to February 16, 1951 he stated that he felt weak, but he was afebrile and the spleen was not palpable. The titer of Brucella agglutinins was 1:160 and blood cultures

*The ACTH was supplied through the courtesy of Doctor Harley Cluxton, Jr. of Armour & Co.

failed to show any growth on February 9 and 15. He was readmitted to the hospital on March 12, 1951 because he became fatigued so readily. He also admitted overindulgence with alcohol. His titer of agglutinins was ± 1:160 on March 14, but agglutinins were absent on March 19 and March 22. Specimens of blood obtained on March 13, 14, and 15 remained sterile.

Beginning on March 15 he was given 20 mg. of ACTH subcutaneously four times daily for one week. While there were no objective changes, the patient did comment upon his increase in strength. There was no significant change in his leukocyte count or in the erythrocyte sedimentation rate. On the sixth day of treatment a Brucella skin test was done with 0.1 ml. of a 1 to 100 dilution of carbohydrate (Lederle). This preparation usually elicits an immediate type of local response, and a fairly severe delayed type of local reaction. However, in this patient the anticipated immediate reaction was absent and only a moderate reaction of the delay type was observed. A skin test was performed simultaneously with heat-killed Brucella cells (Sharp and Dohme). Again, only a moderate delayed type of reaction was noted. He was discharged from the hospital on March 27, 1951 feeling well. Four specimens of blood drawn while receiving ACTH and after discontinuing the hormone remained sterile. When seen on June 25, 1951 he was afebrile and well. The titer of Brucella agglutinins was ± 1:160 and two blood cultures remained sterile.

Comment: It was difficult to ascertain whether this patient was suffering from active brucellosis at the time he received ACTH, or whether his complaints represented the residuals of a preceding infection. The data at hand suggested the later possibility. ACTH was given to this patient who had a history of a duodenal ulcer. As a result of further experience with cortisone and ACTH in other diseases complicated by a duodenal ulcer, it is doubtful whether ACTH would have been used in this patient. The primary complaints in this patient were weakness and easy fatiguability on effort. Coincident with the administration of ACTH these symptoms subsided and he has remained well.

Patient 2, ..., a 30 year old meat packing plant employee was admitted to the hospital on March 6, 1951 because of chills, fever, sweats and weakness of one month's duration. He had been employed loading condemned beef into a "hasher". His own physician had treated him briefly with aureomycin, which was followed by temporary improvement. The physical examination revealed a temperature of 103° F., cervical adenopathy and bilateral testicular tenderness. The titer of Brucella agglutinins was 1:640, and Br. abortus was recovered from the blood on March 11, 1951. Sterile blood cultures resulted on March 9 and 10 and on March 14 he was given 25 mg. of ACTH subcutaneously four times daily, which was continued for a total of 10 days. No outstanding objective or subjective changes were noted during this time, but the patient did improve, and seven cultures of blood taken during and after the completion of treatment remained sterile. There was no significant change in the agglutinin titer. He had remained well when seen 30 days later, and he was afebrile. The agglutinin titer was 1:640, and three blood cultures taken on three successive days remained sterile.

Comment: This patient is of unusual interest because his illness was acute, the presence of bacteremia was demonstrated, and he had a mild, but definite orchitis. While receiving ACTH the orchitis subsided and he became afebrile. Brucella organisms were not recovered from the blood, and immediately following the cessation of treatment he did not have a relapse.

Patient 3, , a 34 year old white farm hand entered the hospital on March 26, 1951 because of chills, fever, sweats, headaches, weakness and epigastric distress of about three months' duration. Two weeks prior to his illness he had fractured his right ankle. He had

ingested unpasteurized milk on the farm where he was employed where one of the cows had aborted. On physical examination the temperature was 98.6° F. and the right ankle was swollen and stiff. Brucella agglutinins were present in a titer of 1:640, and three consecutive blood cultures remained sterile prior to his receiving 25 mg. of ACTH subcutaneously four times daily for 10 days. He remained afebrile during this time, and gained nine pounds in weight. While no pitting edema was noted, after the administration of ACTH was discontinued a diuresis occurred, and he lost all this gain in weight. Ten cultures of blood taken during and after the completion of treatment remained sterile. There was no significant alteration in the titer of agglutinins. When he left the hospital on April 13, 1951 he felt well.

He returned to the hospital on May 28, 1951 complaining of weakness and epigastric distress. He was afebrile and there were no physical abnormalities except evidence of a poorly uniting fracture. The titer of Brucella agglutinins was 1:640, and five blood cultures remained sterile. Serologic tests for syphilis were positive and he admitted having primary syphilis and treatment with two long courses of "arm and hip" injections in 1925-26. The cerebrospinal fluid was normal, chemically and serologically. On June 1, 1951 he suddenly complained of interscapular and substernal pain with a fever of 100.6° F. A roentgenogram of the chest revealed minimal pleural effusion on the left, which disappeared shortly. Electrocardiograms showed transient and slight changes in the T waves. Roentgenograms of the right ankle showed poor union of the fracture of the external malleolus. He was given 0.5 gm. of aureomycin four times daily from June 14 to June 27, and 300,000 units of penicillin intramuscularly twice daily from June 17 to June 27. A brace was fitted for the right leg and he felt well when he left the hospital on June 29, 1951.

Comment: There is little doubt that this patient had active brucellosis even though Brucella organisms were not recovered from his blood. It is difficult to evaluate the effect of ACTH on his illness, except to state that coincident with its administration at least temporary improvement occurred. The subsequent chest pain and laboratory data suggest a pleuro-pericardial inflammation, the nature of which remained obscure. Coincident with aureomycin and penicillin he did improve and remain well. One cannot state whether the brucellosis or the ACTH had any influence on the failure of the bone fracture to heal.

Case 4, , a 56 year old white farmer was admitted to the hospital on September 6, 1950 because of headaches, dizziness, chills, fever, sweats and weakness, which had been present for two years. He had ingested unpasteurized milk, and one cow in his herd had recently aborted. Aside from a temperature of 100.2° F., no physical abnormalities were detected. The titer of Brucella agglutinins was 1:640, and Br. abortus was recovered from blood cultures on October 11 and 12. He was given 0.5 gram of aureomycin every six hours for 21 days. His fever subsided and he became asymptomatic. The agglutinin titer just before leaving the hospital on November 10, 1950 was 1:2560.

He returned to the hospital on February 12, 1951 feeling better than he did on the previous admission, but he stated that he had a low-grade fever, cough and diarrhea. In addition, he was excessively fatigued. On examination he was afebrile and no unusual physical abnormalities were apparent. The titer of Brucella agglutinins was 1:640, and six cultures of blood taken on consecutive days remained sterile. He was given 25 mgs. of ACTH subcutaneously four times daily for 14 days. During this period he was afebrile and a mild euphoria presented itself. Just prior to administering ACTH his hands were noted to be cold and clammy, and a mild tremor was noted.

These features are quite commonly associated with chronic brucellosis in our experience. These manifestations subsided while he was receiving ACTH. Nine blood cultures remained sterile during and after the course of ACTH. There was no significant alteration in the titer of the Brucella agglutinins. He left the hospital feeling well, but two days later severe weakness appeared and he had a marked tremor of his hands. His temperature rose to 99.6° F. He was readmitted to the hospital on April 10, 1951. There were no abnormal physical findings. The agglutinin titer was 1:160, and two blood cultures were sterile. He was started on 0.5 gram of aureomycin orally every six hours and dihydrostreptomycin was administered simultaneously in a dose of 0.5 gram twice daily. Treatment with both drugs were continued for only 12 days, because during this time weakness, anorexia and hostility occurred, and an eosinophilia of 12 per cent was detected. These features abated when treatment was discontinued. During and after this therapy four blood cultures remained sterile. The titer of agglutinins was 1:320 at the conclusion of treatment. He left the hospital on May 7, 1951. He was recalled on August 7, 1951. During the intervening time he had felt well. At this time the titer of agglutinins was 1:80, and a blood culture was sterile.

Comment: This is a remarkable case because the patient had been chronically ill for two years, and at the end of this time Br. abortus was recovered from his blood on two occasions. While aureomycin did cause a definite improvement in his condition, a relapse without demonstrable bacteremia did occur. Subsequently, he did feel better while receiving ACTH, but when the administration of hormone was discontinued, he had a relapse of his symptoms. Although his blood cultures remained sterile, and the titer of Brucella agglutinins had declined, it was concluded that he had a relapse of his disease. Combined treatment with aureomycin and dihydrostreptomycin apparently provoked drug hypersensitivity with systemic manifestations. Following the cessation of treatment with these drugs he felt better, and he has remained well since.

Case 5, , a 35 year old white electrician in a meat packing plant first became ill with multiple joint pains in November 1949. This was soon followed by the appearance of fever, chills, nocturnal sweats and fatigue. By February 1950 he was unable to work any longer and he consulted his physician who advised hospitalization for pulmonary tuberculosis because of the appearance of a roentgenogram of the chest. He entered the hospital on February 13, 1950. His temperature was 99.4° F. There were no demonstrable physical deformities. A diffuse type of interstitial pulmonary infiltration was demonstrated but tuberculosis was ruled out after further studies. Brucella agglutinins were present in a titer of 1:320 and Br. abortus was recovered from the blood on two occasions. During his stay in the hospital he had very little fever. He was treated with two grams of chloramphenicol daily for 10 days, which was associated with marked improvement. He left the hospital on March 20, 1950, and he went back to work on April 17, 1950.

He continued to feel well until October 1950 when he had pain in the chest, fatigue, night sweats, backache and nervousness. When examined on November 29, 1950 he was afebrile, and no abnormal physical findings were detected. A roentgenogram of the lungs revealed evidence of interstitial fibrosis unrelated to brucellosis. Agglutinins were present in a titer of 1:320, but a blood culture remained sterile. It was believed that he had a relapse of his illness, and he was treated with two grams of aureomycin daily for two weeks. Again, he felt better. He was then seen on March 21, 1951 at which time he complained of weakness and nervousness; he became fatigued very easily; and he had night sweats and chills occasionally. He was afebrile and a physical examination was within normal limits. His Brucella agglutinins were 1:640 and

blood cultures remained sterile. Beginning on March 28, 1951 he was given 20 mgs. of ACTH every six hours for 10 days. Within 24 hours after starting the ACTH there was a marked difference in his mental attitude. Despondency and depression gave way to a much more optimistic and cheerful person. His appetite increased enormously. He ate twice as much as the average ambulatory patient. He stated that he felt better than he had for many months. During the course of therapy, a skin test was very slightly positive. There was no change in his agglutinin titer and seven blood cultures taken during and after therapy remained sterile. He left the hospital feeling well. He returned the day after complaining of severe pain in his knees and ankles. Morphine administered by his physician gave little relief. When examined, the joints or overlying tissue manifested no changes. Four days later, without treatment, the discomfort had disappeared. He still felt well. He has remained in good health and at work for nine months.

Comment: This patient with bacteriologic proved brucellosis apparently had a relapse of his illness after treatment with chloramphenicol, and then after aureomycin. He was considered to have chronic brucellosis. Of all the individuals with a more chronic type of illness, this patient made the most dramatic response.

Patient 6, , a 34 year old white farmer, was hospitalized December 23, 1951. His illness began about November 1, 1951 with chills and fever to 104° F. His physician prescribed aureomycin by telephone. Chills and fever continued and he was hospitalized five days later. Nausea, vomiting and low back pain were noted. Aureomycin and penicillin were given and he became afebrile after four days. At home he worked but felt weak. About November 25, 1951 there was a recurrence of chills and fever up to 104° F. He was placed in his local hospital for seven days, and he received aureomycin and penicillin, after which he became afebrile. However, daily chills and fever returned again on December 20, 1951.

The patient was a tenant farmer with a rather large herd of high-grade dairy cattle. There had been no abortions in the herd for at least three years, but he had assisted the local veterinarian in vaccinating the calves twice yearly with live strain 19 Br. abortus vaccine. The herd had not been recently tested for Bang's disease. He drank only pasteurized milk.

On December 23, 1951 physical examination disclosed a well nourished, acutely ill man with a temperature of 101.4° F. His liver was palpable 4 cm. below the right costal margin and was moderately tender. The spleen was not palpable. There was no jaundice. Laboratory studies were as follows: 5,000 leukocytes with 52 per cent neutrophiles and 46 per cent lymphocytes and sedimentation rate 15 mm. in one hour. Brucella aggultinins were present 1:1280+2560. Venous blood cultures yielded Br. abortus on the 24th, 25th, 26th, 27th, 28th, and 29th, of December. Subsequent blood cultures have not been reported as yet. Liver function studies showed 10 per cent bromsulfalein retention, normal serum bilirubin and prothrombin time, 2+ cephalin flocculation (48 hr.), 7.6 units thymol turbidity and 12.9 units zinc sulfate turbidity. A sternal bone marrow biopsy on December 27 revealed multiple immature granulomas. A liver biopsy on the same date showed localized areas of fibroblasts, lymphocytes and epithelioid cells indicative of granulomatous inflammation.

ACTH was given in doses of 25 mg. intramuscularly every six hours for 11 days beginning on December 27, 1951. His fever returned to normal within 15 hours after the first dose and never rose above 100° F. thereafter. He noted immediate improvement although he continued to have sweats and was listless until December 31. He was ambulatory by January 2, 1952. The liver was notably smaller and less tender by December 31, 1951. A skin test with Brucella carbohydrate antigen

(1-100) showed only a slight immediate reaction on January 3, 1952 with 2 cm. of erythema. The lack of fever and the decrease in size and tenderness of the liver in spite of continued bacteremia were most striking. While he was receiving ACTH the leukocyte count rose from 3600 with 54 per cent neutrophiles to 7600 with 82 per cent neutrophiles. The sedimentation rate declined to normal. Liver function tests showed no significant change. Bone marrow and liver biopsies and cultures for Brucella at the conclusion of therapy are not reported as yet. The Brucella agglutinin titer was unchanged. At the conclusion of the treatment the patient was afebrile, felt well and had no physical abnormalities.

Comment

ACTH was administered to four patients (No. 1, 3, 4 and 5) who had been ill for 3 to 52 months. These individuals with the more chronic form of brucellosis were all improved while receiving ACTH. However, the objective evidence of improvement was not remarkable except in patient 5. It is of interest that almost immediately after discontinuing ACTH in this individual, there was an onset of severe pain in the knees and ankles without demonstrable evidence of an inflammatory reaction being present. This discomfort disappeared in a day or two. No satisfactory explanation is available at the present time to explain this brief episode of painful joints. In none of the four patients were Brucella organisms recovered from the blood cultures during and after the administration of ACTH. The hormone did not significantly alter the titer of Brucella agglutinins. However, dermal hypersensitivity to Brucella antigen was considerably reduced while ACTH was being given.

The influence of ACTH upon the clinical course of the two patients with acute brucellosis and positive blood cultures was quite pronounced, particularly in patient 6. The latter patient appeared "toxic" with a high temperature. Within 15 hours after the first injection of ACTH the patient felt much better and the temperature approached and remained normal. This improvement occurred, although Br. abortus could still be recovered from the blood. Such a dramatic and rapid change for the better had never been observed with antibiotic therapy. It had been observed repeatedly in seriously ill patients that the administration of aureomycin was followed in 48 to 72 hours by a marked improvement, although the bacteremia persisted. The response of the patients with acute brucellosis to ACTH is much like that which has been observed in other acute bacterial infections, such as pneumococcic pneumonia and typhoid fever[10, 40]. It is of interest that patient 2 had a positive blood culture just before ACTH was administered, and that without any other treatment he apparently has recovered from his disease.

The basic purpose of using ACTH in these patients was not to afford a means of treating this disease, but rather to learn more about the basic disease process. It may be that some light has been shed upon the mechanism whereby improvement has followed the use by others of Brucella antigens and other agents when administered intravenously to patients. This approach to the therapy of brucellosis has been the subject of considerable controversy. Such authorities as Professor M. Janbon of Montpellier University in France, Professor M. Signorelli of Ferrara University in Italy, and Professor W. Löeffler of Zurich have demonstrated that a sharp febrile reaction induced in patients with Brucella antigen or even with preparations of colloidal silver has resulted in prompt improvement and subsequent recovery in persons with acute and chronic brucellosis, many of them having had suppurative complications. These investigators have all remarked that a febrile response was essential for a good result. This abrupt rise in temperature is invariably associated with a systemic reaction, sometimes bordering on a shock-like picture. Is it not

possible that this reaction stimulates the adrenal cortex, and there is an outflow of cortical steroids, which results in an amelioration of the patients' symptoms? This concept should be investigated further. If such were the case, it might be more desirable to administer either ACTH or cortisone for a few days, along with antibiotics, rather than to shock the person with intravenous preparations. Brucella antigens and other agents injected intravenously may provoke serious and dangerous reactions. Brucellosis has also been treated by physically induced, hyperpyrexia, particularly patients having spondylitis[42, 43].

Summary

1. Cortisone was administered to mice, guinea pigs and rabbits having an acute infection caused by Br. suis. The most striking effect of cortisone occurred in mice. A mild infection was converted into a highly fatal disease with the usual granulomatous lesion replaced by one of suppuration and necrosis in which the rapid mutliplication of Brucella organisms took place.

2. Contrary to expectations, and in contrast to the results obtained in animals with acute infections, cortisone did not appear to effect the course of chronic brucellosis in mice, guinea pigs or rabbits. While contisone did suppress dermal sensitivity to Brucella antigens, the steroid did not consistently influence the titer of Brucella agglutinins.

3. Adrenocorticotrophic hormone (ACTH) was administered to four patients with chronic brucellosis, and to two patients with acute brucellosis from whose blood Br. abortus was isolated just before the hormone was injected. ACTH did not alter the course of the chronic disease in any outstanding manner. There were no demonstrable ill effects following its administration. ACTH had a marked effect upon the toxic course of acute brucellosis resulting in a rapid reduction in fever and a feeling of well being, although in one patient the bacteremia persisted during and after treatment. The results in acute brucellosis were the same as were reported for other bacterial infections such as pneumococcic pneumonia and typhoid fever.

4. As a result of the present study, there is little indication for administering either cortisone or ACTH to patients having chronic brucellosis. In view of the favorable influence on the toxic manifestations of acute brucellosis, it might be advantageous to use ACTH, and possibly cortisone, for a day to two in the seriously ill individual along with aureomycin or terramycin simultaneously administered with dihydrostreptomycin. Before such a course of therapy can be adopted for general use further controlled investigations are necessary.

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TABLE I

THE INFLUENCE OF CORTISONE ON ACUTE BRUCELLOSIS IN MICE

A.

Animals pretreated with 1 mg. of cortisone daily for 5 days before being infected with Brucella suis and then treated for 5 more days after being infected. A control infected group of mice was similarly treated daily with 0.04 ml. of sterile physiologic saline solution instead of cortisone, Another control group, but uninfected, was treated with cortisone

Group	Number of Animals	Average Days of Treatment	Average Total Days of Infection	No. of Animals with Brucella in Hearts' Blood at Time of Death	Average Wgt. of Spleens in Grams	No. of Animals with Brucella Cultured From		No. of Microscopic Lesions per 10 Low Power Fields in			
						Liver	Spleen	Liver	Spleen	Kidney	Lung
Infected - Cortisone	20	10	5	0/0	0.055	7/20	8/20	195	0	0	0
Infected - Saline	20	19	15	6/10	0.403	7/20	11/20	9	0	0	0
Uninfected - Cortisone	9	14	0	0/0	0.050	0/5	0/5	3	0	0	0

TABLE I

THE INFLUENCE OF CORTISONE ON ACUTE BRUCELLOSIS IN MICE

B.

Animals pretreated with 0.5 mg. of cortisone daily for 3 days before being infected with Brucella suis and then treated for 7 more days after being infected. A control infected group of mice was similarly treated daily with 0.02 ml. of saline solution instead of cortisone. Another control group, but uninfected, was treated with cortisone.

Group	Number of Animals	Average Days of Treatment	Average Total Days of Infection	No. of Animals with Brucella in Hearts' Blood at Time of Death	Average Wgt. of Spleens in Grams	No. of Animals with Brucella Cultured From		No. of Microscopic Lesions per 10 Low Power Fields in			
						Liver	Spleen	Liver	Spleen	Kidney	Lung
Infected - Cortisone	26	10	7	7/7	0.132	8/22	8/22	87	0	0	2/26
Infected - Saline	9	11	8	7/7	0.368	7/9	7/9	13	0	0	0/9
Uninfected - Cortisone	4	10	0	0	-	0/4	0/4	0	0	0	0/4

TABLE I

THE INFLUENCE OF CORTISONE ON ACUTE BRUCELLOSIS IN MICE

C.

Animals splenectomized one year previously; pretreated with 0.5 mg. of cortisone daily for 5 days before being infected with Br. suis and then treated for 6 more days after being infected. A control infected group similarly treated daily with 0.02 ml. of saline solution instead of cortisone.

Group	Number of Animals	Average Days of Treatment	Average Total Days of Infection	No. of Animals with Brucella in Hearts' Blood at Time of Death	Average Wgt. of Spleens in Grams	No. of Animals with Brucella Cultured From		No. of Microscopic Lesions per 10 Low Power Fields in			
						Liver	Spleen	Liver	Spleen	Kidney	Lung
Infected - Cortisone	5	11	6	4/4	-	4/5	-	110	-	1	6
Infected - Saline	4	11	6	4/4	-	4/4	-	27	-	10	8

D.

Treatment with cortisone started at same time that animals were infected with Br. suis. One mg. of cortisone given daily for average of 12 days; control group of infected animals received 0.04 ml. of saline solution.

Infected - Cortisone	10	12	12	0/1	0.069	4/10	5/10	74	0	0	0
Infected - Saline	8	14	14	5/7	0.267	2/8	7/8	16	0	0	0

TABLE II

THE INFLUENCE OF CORTISONE ON ACUTE BRUCELLOSIS IN GUINEA PIGS

A.

Three animals pretreated with 10 mg. of cortisone daily for 5 days, and then one infected with Brucella melitensis, one with Brucella suis, and one with Brucella abortus. Treatment continued with cortisone for 5 more days. Three similarly infected animals treated in same way with saline solution.

Group	Number of Animals	Average Days of Treatment	Average Total Days of Infection	No. of Animals with Brucella in Hearts' Blood at Time of Death	Average Wgt. of Spleens in Grams	No. of Animals with Brucella Cultured From		No. of Microscopic Lesions per 10 Low Power Fields in			
						Liver	Spleen	Liver	Spleen	Kidney	Lung
Infected - Cortisone	3	10	5	0/3	0.92	2/3	3/3	7	0	0	0
Infected - Saline	3	10	5	0/3	0.88	2/3	3/3	1	0	0	0

B.

Animals pretreated with 10 mg. of cortisone daily for 5 days, infected with Brucella suis, and then treated for average of 11 more days. Control group of infected animals treated in similar manner with daily injections of saline solution.

Infected - Cortisone	5	16	11	3/3	1.09	4/5	4/5	4	1	0	-
Infected - Saline	5	19	14	3/5	2.80	5/5	5/5	9	13	0	-

TABLE III

THE INFLUENCE OF CORTISONE ON ACUTE BRUCELLOSIS IN RABBITS

A.

Three animals pretreated with 12.5 mg. of cortisone daily for 5 days, and then one infected with Brucella melitensis, one with Brucella suis, and one with Brucella abortus. Treatment with cortisone continued for 5 more days. Three similarly infected animals treated in same way with saline solution.

Group	Number of Animals	Average Days of Treatment	Average Total Days of Infection	No. of Animals with Brucella in Hearts' Blood at Time of Death	Average Wgt. of Spleens in Grams	No. of Animals with Brucella Cultured From		No. of Microscopic Lesions per 10 Low Power Fields in			
						Liver	Spleen	Liver	Spleen	Kidney	Lung
Infected - Cortisone	3	10	5	3/3	1.13	3/3	3/3/	53	0	-	-
Infected - Saline	3	10	5	3/3	2.15	3/3	3/3	9	0	-	-

B.

Animals pretreated with 12.5 mg. of cortisone daily for 5 days, infected with Brucella suis, and then treated with cortisone for 14 more days. Infected control group treated in similar manner with saline solution.

Infected - Cortisone	5	18	13	4/4	1.55	4/4	4/4	27	48	0	-
Infected - Saline	5	19	14	5/5	8.12	3/5	4/5	23	40	0	-

TABLE IV

THE INFLUENCE OF CORTISONE ON CHRONIC BRUCELLOSIS IN MICE

A.

After being infected with Brucella suis one month previously animals injected with 1 mg. of cortisone daily for average of 11 days. Control infected animals treated in similar manner with saline solution for 14 days.

Group	Number of Animals	Average Days of Treatment	Average Total Days of Infection	No. of Animals with Brucella in Hearts' Blood at Time of Death	Average Wgt. of Spleens in Grams	No. of Animals with Brucella Cultured from		No. of Microscopic Lesions per 10 Low Power Fields in			
						Liver	Spleen	Liver	Spleen	Kidney	Lung
Infected - Cortisone	12	11	41	0/0	0.101	1/12	0/12	10	0	0/12	0/12
Infected - Saline	12	14	44	1/11	0.176	2/12	4/12	7	0	2/12	1/11

B.

Mice that had been infected with Brucella melitensis, Brucella suis, or Brucella abortus 10-12 months previous to receiving 4 mg. of cortisone daily for average of 9 days, or 0.16 ml. of saline solution for average of 14 days. Two uninfected control mice received 4 mg. of cortisone daily for average of 11 days.

Infected - Cortisone	11	9	10-12 mos.	0/1 *	0.122	2/11	3/9	5/11	0	0/11	0
Infected - Saline	11	14	10-12 mos.	1/8 *	0.304	2/11	0/9	4/11	0	3/11	0
Uninfected - Cortisone	2	11	-	*Blood from tail	0.040	0	0	0	0	0	0

TABLE V

THE INFLUENCE OF CORTISONE ON CHRONIC BRUCELLOSIS IN GUINEA PIGS

One guinea pig infected with Brucella melitensis, one with Brucella suis, and one with Brucella abortus. After one month animals were treated with 10 mgs. of cortisone daily for 14 days. Three control animals infected similarly were treated with saline solution.

Group	Number of Animals	Days of Treatment	Days of Infection	Brucella From Hearts' Blood		Average Wgt. of Spleens in Grams	No. of Animals with Brucella Cultured from		No. of Microscopic Lesions per 10 Low Power Fields in			
				Before Treatment	After Treatment		Liver	Spleen	Liver	Spleen	Kidney	Lung
Infected - Cortisone	3	14	42	2/3	2/3	3.23	2/3	2/3	3	3	0	-
Infected - Saline	3	14	42	1/2	0/2	4.39	3/3	3/3	9	0	0	-

TABLE VI

THE INFLUENCE OF CORTISONE ON CHRONIC BRUCELLOSIS IN RABBITS

A.

One rabbit infected with Brucella melitensis, one with Brucella suis, and one with Brucella abortus. After one month animals were treated with 12.5 mgs. of cortisone for 14 days. Three control animals infected similarly were treated with saline solution.

Group	Number of Animals	Days of Treatment	Days of Infection	Brucella From Hearts' Blood		Average Wgt. of Spleens in Grams	No. of Animals with Brucella Cultured From		No. of Microscopic Lesions per 10 Low Power Fields in			
				Before Treatment	After Treatment		Liver	Spleen	Liver	Spleen	Kidney	Lung
Infected - Cortisone	3	14	42	2/3	1/3	1.83	0/3	0/3	3	0	0	-
Infected - Saline	3	14	42	2/3	0/2	2.44	2/3	1/3	1	2	0	-

B.

After being infected four months previously with Brucella abortus, animals injected with 12.5 mgs. of cortisone daily for 14 days. One control animal similarly infected treated with saline solution.

Infected - Cortisone	3	14	137	0/3	0/3	0.90	0/3	0/3	0	0	0	-
Infected - Saline	1	14	137	1/1	1/1	1.53	0/1	0/1	0	0	0	-

TABLE VII

PERTINENT DATA OF PATIENTS WITH BRUCELLOSIS GIVEN ACTH

No. of P't.	Age & Sex	Occupation	Duration of Symptoms Before Receiving ACTH	Laboratory Data				Dose of ACTH	Result
				Before ACTH		During & After ACTH			
				Brucella Agglutinins	Blood Culture	Brucella Agglutinins	Blood Culture		
1.	28 Male	Farmer	9 months	1:1280 1:1280 1:320 1:160 [±1:160]	+Br.abortus + " " 0 [0,0,0,0]	+1:160	0,0,0,0	20 mgs. 4 times daily for one week.	Improvement; increase in strength; no relapse; nine months later working. Mild complaints.
2.	30 Male	Laborer in meat packing plant	6 weeks	[1:640]	±Br.abortus	1:640	0,0,0,0 0,0,0	20 mgs. 4 times daily for 10 days	Improvement; no relapse; good health 9 months later.
3.	54 Male	Farmer	3 months	[1:640]	[0,0,0]	1:640	0,0,0,0 0,0,0,0 0,0,0,0 0,0	25 mgs. 4 times daily for 10 days	Improvement; relapse of symptoms in 2 mos. Had positive serology for syphilis and fracture right ankle.
4.	56 Male	Farmer	52 months	1:640 1:2560 [1:640]	+Br.abortus + " " [0,0,0,0,0,0]	1:160 1:320	0,0,0,0 0,0,0	25 mgs. 4 times daily for 14 days.	Improvement; relapse in few days. Given aureomycin Ten mos. later working -- still has aches and pains.
5.	35 Male	Electrician in meat packing plant	16 months	1:320 1:640 1:320 1:640 1:320 [1:640]	+Br.abortus + " " [0,0]	1:1280 1:1280	0,0,0,0 0,0,0	20 mgs. 4 times daily for 10 days.	Marked improvement; no relapse; good health 9 mos. later.
6.	34 Male	Farmer	8 weeks	[1:1280]	+Br.abortus + " " + " " + " "			25 mgs. 4 times daily for 11 days.	Immediate and marked improvement, although blood cultures remained positive.

[ ] = Laboratory data obtained just prior to administration of ACTH.

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II. MEDICAL SCHOOL NEWS

Coming Events

Feb. 14-16	Continuation Course in Therapy of Cardiovascular Diseases for General Physicians
Feb. 19	Minnesota Pathological Society Meeting; "Physiological and Therapeutic Significance of Levo-Arterenol -- the Principal Hormone of the Adrenal Medulla," Dr. M. L. Tainter, Director, Sterling Winthrop Research Institute, Rensselaer, New York; Owre Amphitheater; 8:00 p.m.
Feb. 25-27	Continuation Course in Clinical Dietetics for Clinical Dietitians
Feb. 26	Special Lecture: "The Epidemiology and Control of Pertussis," Robert Cruickshank; Professor of Bacteriology, the Wright-Fleming Institute of Microbiology, St. Mary's Hospital Medical School, London; Owre Amphitheater; 4:00 p.m.
Feb. 28 - Mar. 1	Continuation Course in Dermatology for General Physicians

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Faculty News

At the invitation of the Department of the Navy, Dean H. S. Diehl is flying to Honolulu aboard the Navy giant transport seaplane, the Mars, to spend four days inspecting medical installations and activities in Pearl Harbor, Honolulu and vicinity, and then return to the United States aboard the hospital ship, USS Repose, which will be carrying patients who have been casualties of the fighting in Korea. Dr. Diehl left January 28 and will return on February 11.

Dr. Robert B. Howard, newly appointed Director of the Department of Continuation Medical Education, left Minneapolis on Monday, January 28, for a tour of some of the centers where outstanding work has been done in postgraduate and continuation medical education. Among other centers he will visit the University of Michigan; Tufts Medical College, Boston; New York University Postgraduate Medical School; and Cook County Graduate School of Medicine, Chicago. He will attend the conventions of the 48th Congress of Medical Education and Licensure and the Associated State Postgraduate Committees of State Medical Societies.

Several members of the Department of Surgery have been taking an active role in cancer education for lay people. Dr. George E. Moore recently spoke to the Women's Club at Hutchinson, Minnesota, at an evening session on the subject, "Our Responsibilities to the Cancer Problem." Dr. Richard L. Varco and Dr. John Lewis have been active in cancer training schools in Brown County and Martin County.

New Minnesota Medical Foundation Members

Albert J. Schroeder, M.D., Minneapolis	William F. Hartfiel, M.D., St. Paul
J. C. Miller, M.D., Minneapolis	Roscoe C. Webb, M.D., Minneapolis
Herman E. Drill, M.D., Hopkins	Lawrence J. Opsahl, M.D., Willmar

III. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

February 4 - 9, 1952

Monday, February 4

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom, Todd Amphitheater, U. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - Physiology Seminar: Effect of X-rays on the Incorporation of P_{32} into Organic Constituents of Mouse Mammary Carcinoma; Halvor Vermund; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Pediatric Seminar; Sixth Floor West, U. H.

4:30 - 5:30 Dermatological Seminar; M-346, U. H.

4:30 - Public Health Seminar; 15 Owre Hall.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater.

Minneapolis General Hospital

7:30 - Fracture Grand Rounds; Dr. Zierold, Sta. A.

10:30 - 12:00 Tuberculosis and Contagion Rounds; Thomas Lowry; Station M.

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

12:30 - Surgery Grand Rounds; Dr. Zierold, Sta. A.

1:00 - X-ray Conference; Classroom, 4th Floor.

1:30 - Pediatric Rounds; Robert Ulstrom; 4th Floor.

Veterans Administration Hospital

9:00 - G.I. Rounds; R. V. Ebert, J. A. Wilson, Norman Shrifter; Bldg. I.

11:30 - X-ray Conference; Conference Room; Bldg. I.

2:00 - Psychosomatic Rounds; Bldg. 5.

3:30 - Psychosomatic Rounds; Bldg. 1; C. K. Aldrich.

Tuesday, February 5

Medical School and University Hospitals

8:30 - Conference on Diet Endocrines and Cancer; M. B. Visscher; 116 Millard Hall.

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:00 - 1:30 Selected Topics, Permeability and Metabolism; Nathan Lifson; 129 Millard Hall.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U.H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Presentation of Cases by Drs. Nessa and Anderson, St. Cloud; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 2:30 X-ray Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Spencer F. Brown; 5th Floor.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station F.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:30 - Infectious Disease Rounds; Dr. Hall.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:00 - Liver Rounds; Drs. Nesbitt and MacDonald.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery Tumor Conference; Conference Room, Bldg. I.

1:00 - Surgery Chest Conference; T. Kinsella and Wm. Tucker; Conference Room, Bldg. I.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

3:30 - 4:20 Clinical Pathological Conference; Conference Room, Bldg. I.

Wednesday, February 6

Medical School and University Hospitals

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-109, U. H.

8:00 - 9:00 Roentgenology-Surgical-Pathological Conference; Allen Judd and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Surgery Case; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Radio-Isotope Seminar; 12 Owre Hall.

1:30 - Conference on Circulatory and Renal Systems Problems; M. B. Visscher; 116 Millard Hall.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.

5:00 - 6:00 Vascular Conference; Todd Amphitheater, U. H.

5:00 - 7:00 Dermatology Clinical Seminar; Dining Room, U. H.

7:00 - 8:00 Dermatology Journal Club; Dining Room, U. H.

8:00 - 10:00 Dermatological-Pathology Conference; Review of Histopathology Section; R. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

3:30 - 4:30 Journal Club; Surgery Office.

Minneapolis General Hospital

8:00 - Pediatric Allergy Rounds; Lloyd Nelson; 4th Floor.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

12:00 - Surgery Seminar; Dr. Zierold, Classroom.

12:30 - Pediatric Staff Meeting; Endocardiofibro-Elastosis; Forrest H. Adams; 4th Floor Annex.

12:30 - EKG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:30 - Pediatric Rounds; E. J. Huenekens and Robert Ulstrom; 4th Floor.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; Conference Room, Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

2:00 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

4:00 - 5:00 Infectious Disease Conference; W. Spink; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, February 7

Medical School and University Hospitals

8:00 - 9:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Heart Hospital Amphitheater.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

12:30 - Physiological Chemistry Seminar; Amino Acid Uptake of Mammalian Cells in Vitro; A. M. Thompson; 214 Millard Hall.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

3:30 - Medicine-Pediatric Infectious Disease Conference; Heart Hospital Auditorium.

4:00 - 5:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Malignant Lesions of the Tonsil; Dale B. Parshall; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Minneapolis General Hospital

8:00 - Pediatric Rounds; Spencer F. Brown; 5th Floor.

8:30 - Neurology Rounds; William Heilig; 4th Floor.

11:00 - Pediatric Rounds; Erling S. Platou; 7th Floor.

1:00 - Fracture-X-ray Conference; Dr. Zierold; Classroom.

Veterans Administration Hospital

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

9:15 - Surgery Grand Rounds; Conference Room, Bldg. I.

11:00 - Surgery Roentgen Conference; Conference Room, Bldg. I.

Friday, February 8

Medical School and University Hospitals

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

Friday, February 8 (Cont.)

Medical School and University Hospitals (Cont.)

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; Studies in Familial Periodic Paralysis; Irvine McQuarrie and Mildred Ziegler; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

2:00 - 3:00 Dermatology and Syphilology Conference; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

3:30 - 4:30 Advanced Neurophysiology Seminar; E. Gellhorn; 111 Owre Hall.

4:00 - 5:00 Dermatology Seminar; W-312, U. H.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

11:00 - Pediatric Rounds; Franklin H. Top; 7th Floor.

11:00 - Pediatric-Surgery Conference; Dr. Wyatt, Forrest Adams; Classroom, Sta. I.

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:30 - Pediatric Rounds; Robert Ulstrom; 4th Floor.

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Microscopic-Pathology Conference; E. T. Bell; Conference Room, Bldg. I.

1:30 - Chest Conference; Wm. Tucker and J. A. Meyers; Ward 62, Day Room.

3:00 - Renal Pathology; E. T. Bell; Conference Room, Bldg. I.

Saturday, February 9

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

Saturday, February 9 (Cont.)

Medical School and University Hospitals (Cont.)

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:30 - Anatomy Seminar; The Biology of Radiation Effects; Berry Campbell; 226 Institute of Anatomy.

Minneapolis General Hospital

8:00 - Pediatric Rounds; George Lund; 5th Floor.

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry, and Staff; Main Classroom.

11:00 - Pediatric Clinic; C. D. May and Floyd Denny; Classroom, 4th Floor.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - Hematology Rounds; P. Hagen and E. F. Englund.