PATHOLOGIC ANATOMY OF HUMAN BRUCELLOSIS*

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Bernhard Bang, in Denmark, in 1897 demonstrated the causal relation of the organism now known as Brucella abortus to the contagious abortion of cattle and called the organism abortus bacillus. In the western hemisphere the cattle disease designated as contagious abortion by practical farmers was shown by Mac-Neal and his co-workers in 1910–1911 to be due to the organism described by Bang. They also amended the nomenclature to establish the specific name abortus for the microbe and cultures of this organism, isolated by them from cattle in Illinois, were utilized by Smith and Fabyan, and by Fabyan in their studies of the pathology of this disease.

Although the experimental study of the pathologic anatomy of brucellosis was begun in this country, the major contributions in human brucellosis have come from abroad. Publications in English have not included illustrations of the granuloma believed to be characteristic of brucellosis; that deficiency and the recent publication of necropsy material prompt this report.

REPORT OF CASE

A 26 year old tractor operator was admitted to the New York Post-Graduate Hospital, December 14, 1937, complaining of unexplained intermittent fever. In May, 1937, while driving a tractor off a truck in a farmyard, the tractor turned over, knocking him to the ground and falling upon his left arm. The forearm was lacerated, and the humerus and radius fractured. Immediate debridement and reduction were done and a plaster spica applied. A week later broncho-pneumonia, verified by x-ray, developed and the spica was removed, to be reapplied 3 weeks after the accident. A month after the accident he was discharged as improved. While in the hospital he was seized

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by an attack of fever, marked perspiration and slight weakness, without chills or vomiting and between June and December, there were about 20 such attacks, the most recent lasting 3 days with a fever of 104.5°F. (40.3°C.). There was no loss of weight. On admission the left axillary lymph nodes were enlarged and the skin dusky, all wounds were healed, and temperature, pulse and respirations were normal. Following admission, however, the temperature progressively rose to 105.6°F. (40.9°C.) and the patient died with signs of cardiac failure, January 27, 1938, after a hospital stay of 45 days.

Soon after admission there was a positive macroscopic agglutination with \textit{Brucella abortus} in dilutions through 1:320. Blood cultures were repeatedly sterile, until the day before death when \textit{Staphylococcus aureus} was found. The Wassermann, Kahn, Widal and Felix-Weil tests were all negative. \textit{Brucella} was not found in the feces or urine. There was a moderate anemia; on admission there were 3,750 white blood cells, 72 per cent of which were polymorphonuclear neutrophiles. When the anemia was most marked there were only 1,300 with unchanged neutrophile count, and 4,150 the day before death.

\textbf{Necropsy:} At necropsy, begun 6 hours after death, there was moderate pial edema and pulmonary congestion. The hilar nodes were not enlarged. There were no striking changes in the gastro-intestinal tract and mesenteric lymph nodes. The congested liver weighed 2300 grams.

The firm congested spleen, 890 grams, had a tense capsule, presented extensive areas of raspberry-red softening and the follicle markings were obscured. There was no evidence of suppuration in the left arm and forearm, with bony union well advanced.

\textbf{Microscopic examination:} There was nothing suggesting bacterial or rheumatic activity in the heart. The liver cells in the congested central areas stained poorly, had indefinite borders, and were disintegrating. In the liver capillaries there were small numbers of giant cells of irregular outline, 3 to 8 times larger than erythrocytes with neutrophile homogeneous cytoplasm. The nuclei, with 2 to 8 overlapping lobes, were deeply basophilic and faintly vesiculated; some were peripherally arranged while a few were centrally placed. In some cells the nuclear chromatin was densely packed. In many cells only a narrow rim of cytoplasm was recognized because of the number and size of the nuclear lobes. None of these cells showed phagocytic activity and they were considered megakaryocytes.

Many of the portal fields were markedly enlarged at the expense of the surrounding liver tissue, the cells of which were atrophic, vacuolated and frayed. The bile ducts were unchanged and the blood vessels packed with erythrocytes and blood pigment granules. The stroma was proliferated, forming granulomas (fig. 1) with many cells of epithelioid type, having round to oval, pale-staining vesiculated nuclei. The infiltrating lymphocytes were numerous and there were also polymorphonuclear leukocytes, both free in the tissues and in the capillaries. Giant cells up to 30, were the most striking feature and were
similar to those described in the sinusoids, but generally larger. Other giant cells had non-lobated nuclei, some were undergoing mitosis, and very few were of the Langhans type. The endothelium of the liver sinusoids was generally unaltered and the Kupffer cells were normally prominent. Centrally, in some lobules, the hepatic cords were necrotic and disintegrating but such areas were not extensive.

Fig. 1. Granuloma of Brucellosis in the Liver; × 340
Most of the numerous giant cells strongly suggest enlarged megakaryocytes, while others are of epithelioid cell character.

The capsule and vessels of the spleen were unchanged except for one large vein with a well-marked area of endophlebitis. In the intima, and lifting the endothelium, there was a cushion-like mass of proliferated stroma (fig. 2) formed chiefly of closely packed epithelioid cells. About one half was necrotic and suffused with red blood cells, and there was surrounding infiltration by lymphocytes. At the periphery of the granuloma there were two multinucleated giant cells similar to those described in the liver. The splenic follicles were greatly reduced in size and number, and many had giant cells similar to those
in the liver. Nuclei of other giant cells more closely resembled those of the few epithelioid cells also present. In the red pulp there were extensive confluent areas of necrosis, overrun by baked blood, blood pigment granules, scattered lymphocytes and giant cells. There were equally large areas of marked congestion and hemorrhage with many giant cells phagocytizing broken-down blood pigment. There were smaller foci of partial necrosis with much free nuclear debris, polymorphonuclear neutrophiles and plasma cells in small numbers, as well as the epithelioid cells. Colonies of cocci were seen only in lumens of smaller vessels. Unfortunately lymph nodes were not preserved at necropsy. There were no significant changes in the pancreas, adrenals, or kidneys. At the sites of fracture there were changes similar to those in the liver and spleen and apparently not the result of the injury. There were large confluent areas of fibrinoid necrosis with both necrotic and non-necrotic phagocytes. These were large mononuclear cells, some with vacuolated cytoplasm, while others had ingested polymorphonuclear neutrophiles and lymphocytes. These apparently arose from the endothelium of the capillary spaces of the delicate fibrous marrow and from smaller areas of the cellular marrow in which there were numerous giant cells with lobated solid nuclei, apparently megakaryocytes, which were also present in thrombi in smaller arteries. Where the

**Fig. 2. Granuloma of Brucellosis in the Intima of a Vein within the Spleen; × 158**

The endothelium is lifted by the granuloma but is not injured.
fibrous marrow was more dense and mature there were non-necrotic peri-arteriolar granulomas formed of epithelioid giant cells similar to those in the liver and spleen, and lymphocytes. There were no striking changes in the brain or hypophysis, apart from vascular congestion. In the testis the tubules had narrowed lumens because of thickening of the lining epithelium. Spermatogenesis was incomplete and no spermatozoa were recognized.

In an attempt to find Brucella pieces of spleen were macerated and inoculated in liver infusion broth and in dextrose. Half the cultures were incubated in an atmosphere reinforced with carbon dioxide. All cultures yielded *Staphylococcus aureus* and were negative for Brucella. Some of the macerated material was injected subcutaneously into a pregnant guinea pig that died within three days without aborting. Brucellae were not recovered from its placenta, material from which was injected into a second pregnant pig with a similar fatality and negative bacterial results.

**DISCUSSION**

No attempt is made to report material already covered by Sharp in his exhaustive review or by Sprunt and McBryde, except where difference of opinion exists. Publications that may have been overlooked, as well as those since printed are included. There is no apparent difference between the melitensis and abortus types of Brucella in ability to produce disease in the experimental animal. In man there are, unfortunately, relatively few necropsy reports in which the infecting organism is named. The human subject is infected by the handling of aborting cattle. My patient was injured while working in a farmyard while unidentified injury is also reported. Drinking raw cow’s milk is held responsible, as well as goat’s milk. In one case, a child played in a stable with, and drank raw milk from aborting cows. Brucellosis is commonly a disease of adults and is rarely reported in children. This has been attributed to several causes: the child may have natural immunity; he drinks pasteurized milk; he does not handle farm animals; his sensitivity has not been heightened by other diseases; the agglutination test is rarely done on children; there may be inadequate agglutinins.

Lesions in experimental animals resemble those seen in human subjects. Fabyan reported a chronic inflammatory focal lesion, largely perivascular, very much like that of tuberculosis and
composed of epithelioid cells, with few lymphocytes, isolated plasma and giant cells; mitoses were numerous. Focal necrosis, common in the livers of some animals, was rarely seen in the lymph nodes. A decade later Jaffé\(^1\) repeated Fabyan's work, producing similar lesions after 6 to 8 weeks. The lesions differed from tubercles in that the epithelioid cells were less compactly arranged, stained less deeply, and were better defined, and there was no central caseation. Phagocyted bacilli were recognized. After 3 to 4 months the granuloma sites were marked by loose, poorly cellular connective tissue. After intratesticular injection there were also nodules in the enlarged spleen and lymph nodes composed of epithelioid cells, or, as Jaffé called them, "pale cells," together with a few megakaryocytes. The liver and kidneys had fewer nodules.

Experimental work has also been reported by Klimmer and Haupt\(^1\), Matzdorf\(^10\), Neberle and Pallaske\(^20\), and most recently by Aiello\(^21\), Rothmann\(^8\), and Signorelli\(^22\). Depending on the allergic state Aiello\(^21\) produced either necrotic hemorrhagic lesions in a state of septicemia, or proliferation of the reticuloendothelium followed by the formation of granulomas which he believed specific for brucellosis. These were composed of epithelioid cells, eosinophiles, a few monocytes, polymorphonuclear neutrophiles and pseudo-Langhans giant cells. In some of the animals of Signorelli\(^22\) the granulomas in bone marrow and extramedullary foci had many giant cells of "polykariocytic and megakaryocytic" type. Almost identical results were obtained with live and inactivated bacteria. The megakaryocytic type of giant cell was phagocytic in the spleen, illustrations of which look like the lesions in the case reported here. Rothmann\(^8\) injected guinea pigs with bacilli cultured from the organs and blood of his human case. After 8 weeks there were epithelioid cell nodules in the lungs, liver and spleen with giant cells having 20 and more nuclei; lymphocytes and plasma cells formed the periphery. In the larger nodules there was necrosis and fibrin deposit. The nodules in the animals were larger, with more giant cells, more connective tissue, and a greater tendency to necrosis than in humans. Rothmann thought the granuloma specific for brucellosis.
In human brucellosis the anatomic findings have been less constant, probably due to numerous varying and uncontrolled factors of allergy, emphasized by Rössle in both this disease and typhoid fever, immunity, dosage and virulence of the microorganisms. No definite pathologic anatomic changes are reported in one case, while many note no distinctive or significant alterations. In one such case there were circumscribed foci of connective tissue, as well as areas of necrosis in the spleen. The former may have represented healed lesions and the latter the response to terminal anergy. Uncharacteristic anatomic changes, similar to those in many other diseases, have been produced in the experimental animal by the intraperitoneal injection of tubercle bacilli as well as India ink. Only after a week did epithelioid cell tubercles appear in the lymph nodes. Similar findings were reported in typhoid fever and were likened to those in brucellosis. In human brucellosis von Albertini and Lieberherr, who referred to the granuloma as a “tuberculoid nodule,” were of the opinion that “... certain cases of Bang’s disease can lead to the picture of a granulomatous affection. In contrast to tuberculosis, however, these cases form the exception.” Allergy, dosage and time intervals apparently play the major roles in the production of the granuloma.

Another feature of the anatomic picture that excites interest is the giant cell. In many cases the giant cell is of the Langhans type, but a few authors call attention to the megakaryocytic character of the cell. Megakaryocytes are not uncommon in vessels in diseases with much bone marrow stress. This exists in brucellosis where destruction and phagocytosis of red cells is a prominent feature. The megakaryocytic giant cells in the granulomas described in this paper were generally larger than the megakaryocytes in the vessels and were definitely multilobated. In one case the giant cells were described as similar to Sternberg giant cells of lymphogranulomatosis. Multinucleated epithelioid cells similar to those also found in my case have been reported.

Changes have been reported in virtually every organ in the body. Bergmark found a chronic meningoencephalitis with
round cell infiltration, especially about some vessels, in the pons and about the Sylvian fissure. Regressive changes were seen in large ganglion cells, in part with disintegration. Brucella was recovered from the spinal fluid in another case where the meninges were studded with "tubercles," formed chiefly of hyalinized connective tissue with chronic inflammatory cells. Earlier stages, including necrosis were seen. A meningoencephalitis comparable to that in typhus has been reported. Throughout the nervous system there were nodules of round cells, plasma cells, leukocytes and especially glial cells. Brunner reported an abscess in the thyroid with Brucella abortus in pure culture, which was also in the blood. Non-specific diffuse fibrosis of the thyroid with "histioid" cells in areas of lymphocytic infiltration has been described. Characteristic lung lesions have been reported only in experimental animals.

Brucella melitensis was recovered from the blood and from a thrombus on the heart valves. Negative blood culture and tissue bacterial findings in a case with marked aortic ulcerative thromboendocarditis are reported, while in another only the culture was positive. In a child there were foci of lymphocytes, a few plasma cells and large cells with kidney-shaped nuclei about the epicardial vessels and diffuse lymphocytic infiltration of the myocardium. "Interstitial myocarditis" was reported in other cases. Rothmann saw subendocardial foci of necrosis surrounded by lymphocytes, epithelioid cells and plasma cells; media and intima of myocardial vessels were necrotic and there were bacteria and fibrin in the lumen. Vascular lesions include a mycotic aneurysm of a cerebral vessel with rupture.

The granulomas believed to be characteristic of brucellosis are most often seen in liver, spleen, or in both, as in the case reported here. Necrosis of the granulomas has been described, chiefly in those without or with but poor formation of giant cells. Specific and non-specific alteration were seen in the same organ. Gall bladder and liver lesions were described by Mettier and Kerr whose paper has the only illustrations of Brucellar granulomas encountered in the English or American literature. The granulomas pictured...
are in a fibrotic stage, however, and fail to reproduce adequately the more characteristic features. Loffler and von Albertini called attention to splenic endophlebitis and thought it produced involvement of the liver through the portal vein, and that brucellosis is therefore chiefly a hepatolienal disease. The infrequency of vein lesions and the virtually obligate splenomegaly prompted von Albertini and Lieberherr later to attribute the major rôle in brucellosis to the spleen. They thought that each attack of fever is produced by an invasion of Brucellae into the blood stream; the organisms come from the spleen and are removed from the blood by the "so-called primary blood filters with their reticuloendothelial apparatus." The absence of characteristic anatomic changes at many necropsies was explained by assuming that such cases are pure bacteremic forms, that the reticuloendothelial apparatus of the filters overcomes the infection, and that as a result granulomas are not formed; hence, the infrequency of granulomas.

Lymph node granulomas were seen in most of the cases with and in some without splenic lesions. The diagnostic problems so commonly presented by lymph node changes are well illustrated by Grumbach's case. His patient, with a positive agglutination (1:640), had a periostitis of the tibia and of a malleolus, and after the lesions softened, Brucella abortus, porcine type was recovered. A similar organism was found in pus from a lymph node. A lymph node, removed at biopsy, was diagnosed as tuberculous by von Albertini, although no tubercle bacilli were seen in the sections and no animal inoculation was done. Bone marrow lesions, as described in my case and similar to those in other organs, have been reported. Sprunt and McBryde called attention to the replacement of normal marrow cells by atypical mononuclear cells, findings generally similar to those of Eyre, while foci of "histioid reaction" in the marrow appear in another report.

The only reference to the adrenals recorded bacteria in the vessels and areas of necrosis. In kidneys, granulomas, some with necrosis, have been described while acute glomerulonephritis was seen by others, once with granulomas.
Non-specific changes are usually not recorded. Apart from the few observations reviewed by Sharp, there are only isolated reports of changes in the genital tract. Wegener, who is the only author describing granulomas in the salivary glands, reported similar lesions in the testis interstitium, and large foci of necrosis in prostate and seminal vesicles. Amoss described the unique case of a woman in whom, at operation, the right oviduct was seen to have lesions resembling those of tuberculosis. From the same oviduct Brucellae were recovered. Two acid-fast bacilli were also seen in several sections of the same organ and material from the tube produced tuberculosis in a guinea pig. Brucellae were also found in small cysts in the ovary, in adjacent lymph nodes, in the appendix, ileocecal lymph nodes and in the lesions of the peritoneum which looked like those of tuberculous peritonitis. The granulomas, histologically, were like tubercles with giant cell and lymphocyte infiltration, but there was less connective tissue than is usually seen in tubercles.

It seems not unlikely, when one considers the relatively few fatalities in brucellosis, that the body is able to destroy the invader. No specific evidence of the invasion is left behind since relatively few necropsies show specific anatomic evidence of the disease. Those patients who die early in the disease show the features that are common to all malignant bacterial diseases. Only the patients in whom the equilibrium of attack and defense continues for months develop the lesion that may be regarded as characteristic. Combined with clinical evidence of brucellosis, the lesion can probably be considered specific.

**SUMMARY**

A 28 year old tractor operator sustained compound fractures of the arm while working in a farmyard. Soon afterward, and continuing until death eight months later, there were repeated attacks of fever associated with anemia and leukopenia. The macroscopic agglutination test with *Brucella abortus* was positive in dilutions through 1:320. At necropy there was general visceral congestion and evidence of continued breakdown of red cells. The bone marrow, enlarged liver and spleen, and the splenic...
vein were sites of granulomas. These consisted of epithelioid cells, lymphocytes and giant cells, many of which were multilobated and resembled enlarged megakaryocytes. The granulomas were similar to those described in the literature, which is reviewed. The relative rarity of findings of granulomas is explained by the comparative case of the body to finally overcome Brucellar infection. Only in protracted illness is the characteristic granuloma formed.

ADDENDUM

Since this work was completed, additional references have been found. Three cases of blood stream infection are reported, one with aortic\textsuperscript{43} and two with mitral endocarditis\textsuperscript{44, 46}. Nicolaewa\textsuperscript{46} described eye changes similar to those seen in syphilis and tuberculosis. One recent report\textsuperscript{47} describes "small nodular lesions" in lungs, liver bone marrow, spleen and lymph nodes, while another\textsuperscript{48} records granulomas in liver and spleen.

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REFERENCES

Owing to their number, references are not printed but will be included in the author's reprints.