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Pathological anatomy of listeriosis, especially in the animal.

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Discourse No. 5, Listeriosis, a symposium at Giessen, Germany, 27-28 June 1957, pp 49-56. Supplement 1 to Zentralblatt für Veterinärmedizin, 1958.

One always expects assistance from pathological anatomy in the clarification of the nature of a disease, no less of an infectious disease, applicable primarily to diagnostic with characterization of the anatomical changes, to the localization of the changes, to incidence in the various animal species and its clinical aspects. In this connection pathological anatomy may frequently give epidemiological pointers.

What is the present situation in regard to listeriosis? There is no doubt anymore about its world-wide dissemination among diverse animal species, about its occurrence in man and thus about its significance as zoonosis.

In respect to natural infections, listeriosis has been observed in rodents such as the rabbit, mouse, guinea pig, rat, in nearly all domestic animals like the sheep, goat, cattle, swine, horse, chicken, canary, dog, also in the fox, mink, mountain-cock, etc.

The clinical and pathologic-anatomical findings have been considered next to the bacteriologic and serologic ones in all publications, making them more or less known, and for this reason the following shall not be a systematic presentation but an attempt to stress the characteristic, the common and also the divergent in the various animal species. ()

The disease form accompanied by the well-known, evident central nervous manifestations reveals rather an unspecific overall finding macroscopically, unless catarrhal-purulent rhinitis and conjunctivitis are present. The leptomeninges may seem slightly thickened and turbid, the cerebral substance somewhat moist. Focal lesions in the leptomeninges and the cerebral substance usually cannot be determined with certainty macroscopically. Histologically, however, in more pronounced central nervous disturbances, distinct lesions are evident either in the form of leptomeningitis only, or more frequently as encephalitis and also myelitis with involvement of the pia. The lesions of the leptomeninges consist of moderate hyperemia, moderate edema and vascular, mainly monocyctic infiltrates, rarely of granuloma-like formations. In the cerebral substance the lesions localize most distinctly in the cerebral peduncle, especially pons Varolii, medulla, corpora quadrigemina, optic thalamus and corpus striatum, also cerebellum and spinal cord. The telencephalon and pallium appear little diseased or not at all. The more unspecific lesions consist of distinct vascular, partly perivascular cell infiltrates of the precapillaries by a majority of monocytes and isolated leukocytes. These infiltrates have the greatest similarity with the virus-caused Borna-encephalitis of sheep and make differential diagnosis difficult for beginners. However, a differentiation from Borna generally succeeds by further observation of cerebral lesions. In the enumerated cerebral sections there are multiple, initially small focal lesions

which frequently tend toward fusion, resulting in alterations over extended areas. They occur in the white, but more often in the gray substance. The histogenesis of the focal lesions can best be determined at fresh foci. Here, under the effect of bacteria demonstrable singly or in groups or as a layer, necrosis of the cerebral substance ensues, with severest changes in the ganglion cells and fibers and simultaneous infiltration by leukocytes which rapidly increase and also succumb to necrobiosis. A distinct gliotic cell reaction in the foci proper is lacking. However, in the remaining islands of cerebral substance between the focal lesions an activation of glia cells is noted. Accordingly, we are dealing here with the signs of an encephalitic reaction of a purulent nature, usually with involvement of the leptomeninges. It points from the start to a bacterial infection in contrast to virus-caused encephalitis of a non-purulent nature. The severe and extensive lesions of the cerebral substance proper generally allow an easy differentiation of listeria-encephalitis from Borna-encephalitis. The focal lesions in the cerebral substance, histologically speaking, may not so much be characterized as true granuloma (with few exceptions) than as purulent-necrotizing focal encephalitis. I was able to observe the beginning of recovery. At later histological examinations primarily smaller gliotic foci without bacteria were found.

In the other form of sheep listeriosis of gravid sheep, abortions, premature births or terminal births with weak newborn without nervous disturbances occupy the foreground. Pathological-anatomically speaking, the occurrence of metritis and retentio is frequently recorded, generally without evident illness on the part of the ewe, a reason for the circumstance that hardly any certain observations of the pathologic-anatomical nature of uterine lesions exist. The fetuses are edematous or mummified. The pathogen may be cultured from the organs, even from the contents of the abomasum. The literature hardly mentions anything about focal lesions in sheep fetuses. I should like to assume, however, proceeding from general experience, that here too at least submiliary, only histologically visible foci may exist, especially in the liver. Detailed pathologic-anatomical examinations of the uterus, as well as the mammary gland, fetuses, placenta are still lacking in sheep and absolutely must be conducted in the future along with bacteriologic tests. It is known that pregnant sheep will abort when infected intravenously or orally (Paterson, Gray et al.)

Septic forms of illness seem to be rare in sheep, but have been observed in lambs with hepatic foci. In one encephalitically afflicted lamb I found necrotizing focal pneumonia with strong cellular demarcation and massive listeria in an apical lobe of the lung. It is possible to create a septic disease picture with moderate swelling of the spleen and miliary foci in the liver and spleen by intravenous and also by intracerebral infection, especially in lambs.

Bovine listeriosis also reveals an encephalitic and a metritic form with abortions and still births, reports on the latter being somewhat more frequent than the first. The pathologic-anatomical changes of the encephalitic form correspond to those of sheep, as far as data is available; the reader is referred to them. The form occurs in calves as well as in adult cattle (L. Guerden and A. Devos and others). So-called recoveries with retention of postencephalitic manifestations do occur. Gray and Moore found hyalinization in the cerebral substance and cicatricial processes (see Pallaske in connection with sheep). Since we know that in connection with the etiologically inadequately understood

virulent catarrhal fever in cattle an encephalitic reaction in the sense of non-purulent encephalitis is frequently noted histologically, pertinent reports by Beller and Zeller concerning demonstration of listeria in the brain and in creep membranes of such animals have a special significance; the question must be clarified further.

Exact pathologic-anatomical data on the changes in the genital apparatus, even when accompanied by abortion, in bovine listeriosis are very meager, since the abortion is generally overcome without important disturbances in the cow. Thus, as in the case of sheep, we usually speak of metritis and endometritis, accompanied by retentio, respectively. Jedie observed septic metritis in connection with a listeric abortion leading to slaughter, a characterization tending to indicate that weighty uterine affliction with sepsis may also occur here. Similar data may be inferred from Ozgen's report. According to information released by Hartwick and Renk in connection with a case of listeriosis with still birth and later slaughter, an ichorous exudate and adhering shreds of the amnion were found in the cervix and the pregnant horn. In placentoma, irregularly formed disintegrating centers, partly with inflammatory demarcation, as well as bacterial clots in the vessels were determined histologically. The after-birth was edematous and revealed dirty necrobiotic areas. Lesions in the mammary gland were limited to (in places) scanty interstitial inflammatory infiltrations. Listeria could not be obtained from it. Other organic lesions were also lacking. On the other hand, mastitides whose nature has not been characterized more closely pathologic-anatomically, have been observed with findings of listeria.

More precise pathologic-anatomical data exist on bovine fetuses. They show in part subcutaneous edema, in part they also appear in a condition similar to mummification, probably if they died some time prior to abortion. Since bacteriologically the pathogen may be isolated from the majority of organs, pinhead-sized focal necroses may be found, especially in the liver, less frequently in the spleen, kidney and lung, at times bacterial aggregations in the vessels. Accordingly, the fetus as a rule is involved in a septic general affliction. According to Gray, similar septic disease pictures are observed in infected, almost fully developed calves born dead or with a low vitality. Here, too, bacterially caused hepatic necrosis and gastroenteritis and thromboendocarditis may be determined. The hepatic necrosis occasionally seen here, which extends over entire lobar groups, in my opinion develops secondarily due to vascular thrombosis in the wake of vascular collapse of the bacterial necrosis and also due to development of intimal granuloma. Also important are the findings of Rubarth and Wollarz who found miliary necrosis caused by listeria in the liver of 250 weaning calves in connection with bacteriologic meat examinations, representing evidence for the probability of high incidence of listeria in calves. Septic listeric disease may also be induced experimentally in calves. In cattle listeriosis occasionally progresses with abortion and simultaneous encephalitic manifestations (Smith, Reynolds and Bennett). No certain pathologic-anatomical data exist to date on the bull, especially on lesions in his genital apparatus.

Concerning listeriosis in goats, some reports are available, even though scanty. Encephalitic forms and those with loss of the kid occur, in which the abortion usually takes place in the last month without particular signs of disease in the she-goat. However, septic necrotizing metritis leading to death

has also been described.

In connection with swine listeriosis, primarily encephalitic forms with tremor, coordinational disturbances, paresis, cramps (especially in young swine, weaning sows and sucklings). Since inflammatory cerebral lesions occur in swine in connection with plague, enzootic poliomyelitis suum and due to other, as yet not understood causes, listeriosis takes on differential diagnostic significance. In other cases it may progress in septic forms with pneumonia and septic dissemination of bacteria in the organs with necrosis, especially of the liver, spleen and kidneys (Ryu).

Some observations also exist on listeriosis of the horse, in which encephalitic symptoms take the lead. Even in Borna-encephalitis listeria were several times isolated from the cerebral substance. These cases require a recheck, however, in view of the involvement of Borna virus. In addition, keratoconjunctivitis and stomatitis were observed. Nothing is known of listeric disease with loss of the foal. On the other hand, cases with septic symptoms in the foal have been seen. It is said that horses cannot be infected artificially.

Few reports exist on canine listeriosis; they describe primarily central nervous disturbances resembling distemper. Here, too, the significance of listeria must be clarified further, not only in relation to the so-called nervous form of distemper, but to all forms of distemper. The same applies to distemper of farm foxes and mink. Dogs and cats also are said to be non-infectible experimentally; this claim must be subjected to recheck, however.

aside from that of sheep, listeriosis of the chicken became known earliest. Pathologic-anatomically the most pronounced signs are yellowish-white foci and nodules permeating the myocardium. A few times I found serofibrinous pericarditis besides, so that the pericardium represented a flabby sack with an amber-yellow liquid. In some cases I was able to see, in addition to the myocardial lesions, miliary and submiliary necrotic foci in the liver and spleen, often only histologically. Consequently we are dealing with a subacute septic form of listeriosis in the chicken. In artificially infected chickens the same conspicuous myocardial foci and miliary necrosis of the liver occur. The myocardial foci prefer the left ventricle and the septum. Histologically minute and larger foci tending toward confluence may be noted. In the most recent foci one can still see the severe fiber damage up to necrosis imbedded in areas of nuclear debris of inflammatory-reactive cells. In the larger foci not even fibrous remains can be seen anymore. They consist of cell aggregations whose character cannot be determined in the center due to necrosis with nuclear pycnosis and nuclear lysis. Farther out necrobiosis, primarily of monocytic cells, predominates. Peripherally the reactive inflammation radiates for varying distances between the muscle fibers. Primarily histiocytic cells are found here, which sometimes take a whorled position around the focus and occasionally develop a few giant cells. Still further on the edge of the foci an inflammatory-edematous interstice may encroach on the epicardium and may lead to serofibrinous pericarditis. With their peripheral proliferating processes the foci resemble those of a pullorum infection, in which the strong regressive alterations of listeriosis are missing, however. Few bacteria are found in the myocardial foci, more in possibly existing organ necrosis. The central nervous system has not yet been subjected to detailed examination. At times listeria may be isolated from a

degenerate ovary and as a bacterial accompanying phenomenon in other diseases of the chicken (leukosis, Newcastle disease). In turkeys, ducks, geese, canaries, mountain cocks, myocardial foci or septic findings have been determined. Pigeons are frequently said to react refractorily to infective attempts.

Concerning rodents, listeriosis research after all started with them (Murray, Webb and Swann). Even though rodents represent the primary test animal, enzootic disease on test animal farms is almost unknown, except for the outbreak at Cambridge some time ago. On the other hand, enzootic listeriosis has been known for a long time to exist among stocks of rabbit breeders and on rabbit farms, e.g. among chinchillas on Canadian and North American farms. In Germany there are reports by Traub, Schoop on Angorra rabbits, by Mayer, Hellmann and Taubrich on chinchillas. Clinically and pathologic-anatomically the encephalitic and metrogenic forms predominate. The latter often shows a septic character. In the first case pathologic-anatomically a subacute purulent meningoencephalitis develops, according to Traub frequently with involvement of the middle ear. According to my own experiences it may be duplicated by intracerebral infection, and then also progresses septicly with miliary foci, usually in the liver. All evidence points to the predisposing significance of pregnancy for infection. In this case the metrogenic form is preferred, revealing in total agreement purulent endometritis or metritis or pyometra with peri- and parametritis, less frequently endometritis simplex. The fetuses are dead, sometimes with commencing purulent fusion. Abortions are rare. Generally septic metritis is involved, a view supported by encroachment on the peritoneum and focal lesions, especially in the liver and kidney. Histologically the foci represent partly more necrosis, partly more necrotizing granuloma.

The rabbit is also well suited as a laboratory animal. The intravenous infection as a rule leads to granulomatous sepsis. Following subcutaneous and particularly submucous infection frequently severe local inflammatory swelling ensues, partly with purulent fusion and strong disturbances of the general condition (W. Osebold and T. Inouye); experimental keratoconjunctivitis may also be effected (Murray).

Guinea pigs show a somewhat uncertain behavior in infective attempts. However, even here a generalized infection succeeds, with necrosis in the liver and the adrenal glands, occasionally bacteria-containing necrosis of the cardiac muscle as in the chicken.

Rats are often somewhat resistant. According to all experiences, mice are best suited as test animals. Of the diverse methods the intraperitoneal infection, according to Flamm, is the most successful, resulting in death within 6-8 days at the latest and revealing generalized disease symptoms. The liver shows the formation of foci most distinctly, which in early death cases consist of bacterial necrosis, in later deaths primarily of retothelial granuloma poor in bacteria, with central necrosis. In addition there may be miliary necrotizing granuloma in the spleen, adrenal glandular necrosis, subepicardial myocardial necrosis, pleural granuloma and even meningoencephalitis. According to Webb the peritoneal exudate possibly forming after intraperitoneal infection may be rich in leukocytes and macrophages containing listeria, and may also reveal mesenteric glands and changes in the reticulum. The same author also mentions pulmonary foci of the character of hepatic necrosis in connection with

rodents, also a few giant cells of the Langhans type phagocytic for listeria, so that similarity exists with tubercular foci.

In rodents especially, other infectious diseases with miliary focal lesions in the liver and spleen play a differential-diagnostic role, at least macroscopically. The frequent so-called pseudo-tuberculosis of rodents (Pest. pseudo-tuberculosis), salmonellosis, tularemia and moniliosis need only be mentioned. Pseudo-tuberculosis may be differentiated macroscopically by the overall findings with frequently nodular and ulcerative intestinal lesions, distinct swelling and also necrosis of the mesenteric lymphatic gland, histologically by copious bacteria in the necrotic centers already visible by ordinary H&E staining. Furthermore, there is no need to linger on the pathologic-anatomical differential diagnosis in detail, since the demonstration and differentiation of listeria no longer offers any difficulties.

If the animal forms of listeriosis in their totality are viewed from the pathologic-anatomical standpoint, the multiform morbid processes nevertheless are dominated by certain disease symptoms. As shown, they may entail forms that are meningo-encephalitic, further -- metrogenic with or without abortion, premature births or births of mature young with low vitality, finally septic forms with focal lesions characterized by infectious granulomatosis which may be found in all organs, but particularly in the liver, spleen and kidney. These forms may be in competition in one animal species with regard to their incidence, in others one or another form predominates in the course of the disease. Grossly one can say that the septic forms predominate in the small laboratory animals, fetuses and young, the encephalitic and metrogenic forms in the larger animals including rabbits. Concerning the diagnosis of these disease forms, no very great difficulties are encountered even pathologic-anatomically, often causing the pathologic-anatomical diagnosis (or at least a strong suspicion) to precede the bacterial. Precisely pathological anatomy has been able to show that the nature of listeric changes in the various animal species correspond to those of man, one is almost tempted to say in the smallest details, in a way that is hardly known to exist in connection with any other common infectious disease of man and beast. Without going into details and without trying to anticipate other reviewers, a comparative observation will show this to apply not only to the focal lesions so typical for this disease (which may occur in the various species as purely proliferative granuloma, listerioma, or as so-called resorptive granuloma with central necrobiosis, or as more or less non-reactive necrosis, forms of focal alteration which may develop side by side depending on differences in virulence, probably even more on different individual and special resistance or disposition, duration of the disease with changes in its course, and exogenically caused decrease in resistance) but also to its organic localization and the observed progressive forms. I should like to refer in this connection to one of the more recent publications of Dr. Eck, the prosector of St. George, Leipzig, on fatal encephalo-myelitic cases of human listeriosis, some of which I was able to examine and compare histologically, and which completely agreed with the encephalitic listeriosis of sheep so well known to me. These closely agreeing pathologic-anatomical conditions in particular point to a similar susceptibility of man and to epidemiological connections.

Now pathological anatomy is asked to furnish contributions to the important questions of pathogenesis and epidemiology, and justly so. Unfortunately nothing

further may be added on the part of animal pathology about the natural infection of different species, for example, since obvious reactions in the sense of primary effects are lacking at the possible portals of entry. Conjunctivitis, rhinitis, anginous processes may be mentioned in this connection. It shall be the mission of pathology among others to examine histologically, more than heretofore, the possible forms of entry -- the nasopharyngeal space, tonsils, lungs, lymphatic glands and the lymphatic apparatus of the alimentary tract. The same applies, in view of the dispersion, to many endometritides heretofore considered unspecific, which cannot be attributed to brucellosis and other pathogens, to abortions and also to unspecific mastitis of domestic animals, if they can be obtained.

The question of the role of listeria must also be pursued in the case of metrorrhagic pathologic-anatomical lesions in the genital apparatus of male animals, of newborn animals with low vitality, of Borna-encephalitis of horses and sheep and other diseases of the central nervous system. In some sheep-Borna outbreaks simultaneous listeriosis has been found. In connection with other infectious diseases it has been shown again and again that the questions of latent, abortive and atypical forms with secretion, of germ carriers and external dispersion may be clarified further by exact pathologic-anatomical examinations.

Histologic examinations, especially in the areas of possible portals of entry, are necessary also for the testing of the significance for diverse pathogenetic questions of bacterial infections with macroscopically inapparent lesions but already with histologically visible retothelial reactions. We know of a number of infectious diseases that such macroscopically latent retothelial reactions already represent an expression of a biological reciprocal effect between pathogen and body, which already cause formation of antibody and thus serologic reactions, and occasionally under changing effects are a preliminary condition for the manifestation of disease.

Considering the experiences of pathology I would assume that in listeriosis the bacteria do not enter at some spot completely without reaction and without difficulty enter the blood stream, but that initially there is a retothelial defense (even if weak) at the portal of entry, leading to lymphogenic resorption and finally to lympho-hematogenic metastatic dissemination in the body, unless an injury allows direct entry into the blood. This process is dependent on the reactional situation in the form of granuloma or necrotizing granuloma or necrosis. Findings of bacteria without focal lesions in the organs frequently may be interpreted as a sign of terminal sepsis. The hematogenic mode of dispersal seems indicated by the disseminated focal character and the vascular connections found everywhere. Additional dispersion in the brain may take place by way of the liquor, as in the case of plexal lesions. We assume the diaplaccental mode, i.e. via the parental and fetal placental capillaries in connection with the septic infection of animal fetuses, not excluding the possibility of further infection by excretion into the amniotic fluid. I also admit the possibility, in view of the frequent mention of endometritis and metritis, of an infection of the amniotic fluid due to placental affliction, considering the close anatomical proximity of the placenta materna to the placenta fetalis.

Pathogenetically my experiences force me to conclude that exogenic factors — gross hygienic errors, one-sided (albumin deficiency) or crass alterations in the diet, sudden changes in surroundings, etc. may help in making the infection manifest.

The pathology of animal listeriosis, as that of human listeriosis, still leaves many questions unanswered, which could be of importance primarily to epidemiology. Only combined activity will produce progress, to which the present symposium is a promising introduction.