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AUTHORITY
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Fort Detrick
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The pathogeny of listeriosis.

by H. Flamm

From the Hygiene Institute of Vienna University.

Discourse No. 6, Listeriosis, a symposium at Giessen, Germany, 27 - 28 June 1957. pp 61-65. Supplement 1 to Zentralblatt für Veterinärmedizin, 1958.

The following presentation is an attempt to reconstruct the genesis of infection by *Listeria monocytogenes* by means of existing observations and experiments.

Since the epidemiology and epizootology of listeriosis still leaves many questions unanswered, the origin of pathogeny, the entrance gate of the excitor is obscure. Although we may know the definite location at which listeria entered the organism in one particular case or another, in the majority of cases we must rely on conjecture or a conclusion by analog.

We may maintain with certainty, however, that *Listeria monocytogenes* assumes three roles in relation to the host organ, namely

that of saprophyte
that of excitor of local disease processes and
that of sepsis excitant.

The primary responsibility for local or general disease in the immediate wake of listeria infection is to be ascribed to the relative virulence of the excitor, whereas decrease in resistance of the infected body is decisive in later onsets of illness.

If the germs are not sufficiently virulent to trigger a disease immediately upon meeting with man or beast, they are killed and expelled. Occasionally they remain for varying periods of time as harmless saprophytes in the host organism. If a decrease in the host's resistance occurs during this time, the heretofore harmless saprophytes may cause a disease.

Our experiments with transfer of listeria to rabbit eyes (Flamm and Zehetbauer) give an indication of the importance of germinal virulence. We were unable to effect changes in 8 rabbits with a small infective dosis, aside from a slight chemosis of the conjunctiva, although we had caused lesions of the cornea or the conjunctiva or both in 6 animals. It required a larger dosis to obtain the complete picture of ocular listeriosis in 10 rabbits. Hereby the course of the disease in the scarified eyes set itself apart only by the fact that the acute inflammatory changes occurred faster in the conjunctiva. If the virulence of the listeria has been too low for the applied amount, no disease resulted, notwithstanding the decrease in resistance of the traumatized eyes. On the other hand, this condition was unable to further the intensity of the disease, even with a sufficiently large infective dose.

Bacteriologic findings of listeria as apathogenic saprophytes are well known from the reports of Rhoades and Sutherland, Morris and Norman as well as

Bolin and Eveleth. It is true that in these cases disease did not result in the listeria-harboring animals despite decrease in their resistance, although we would expect the latent listeria infection in animals weakened by accidental illness to lead to manifest disease. Evidently the virulence of these listeria strains which had heretofore lived saprophytically in these animals, was too low to cause an infectious disease, even after the scales had been tipped in their favor.

A pleasing example of the factual development of manifest disease by heretofore saprophytic listeria was contained in the observations of Eveleth et al, who were able to uncover radical changes in feed in the history of many outbreaks of listeriosis on sheep farms. These findings seem to indicate that the germs had led a saprophytic life in the sheeps' intestine over a varying period of time. Such an occurrence, e.g. in the bovine intestine, was proved culturally by Rolle and Mayer. These authors were able to infect mice orally with listeria only upon simultaneous subcutaneous injection of a toxic Coli strain. The same successful experiment was made by Juslin and Stenberg by means of oral instillation of such a Coli strain in feed. Urbach and Schabinski caused fatal infections in guinea pigs by feeding them listeria after long starvation.

The local disease caused by listeria mentioned in second place may develop either at the locale of germinal entry or by their migration in connection with bacteriemia. In involvements of the eye, the naso-pharyngeal space and the deep air passages as well as the gastro-intestinal tract we should be dealing with primary effects. The relatively scanty reports on such findings, which due to the atypical picture only rarely are recognized as listeric manifestations, are listed in the summaries of Seeliger as well as Krepler and Flamm, and discussed in the experimental studies by Flamm and Zehetbauer, as far as the ocular form is concerned.

From these primary foci the listeria invariably travel into the lymphatic passages and cause an inflammation of the regional lymphatic glands. This is strikingly demonstrated by two cases of illness observed by van der Schaaf and van Ulsen, involving a farmer and a veterinarian who fell ill simultaneously after assisting in bovine abortions. Starting at an unnoticed injury at the right arm, the listeria penetrated deeply and caused distinctly visible lymphangitis. Later meningitis developed as a sign of generalization.

Experimental explorations by Osebold and Inouye also show a lymphogenic spreading of listeria in the attacked organism. The two authors were able to find the excitors in the regional lymphatic glands and even in the internal organs following application of germs on various mucous membranes of rabbits and sheep.

We must assume that even in most cases of spontaneous infection the listeria overstep the barrier of regional lymphatic glands and reach the blood stream. In this connection it is immaterial whether or not a primary focus had developed in the first place and whether the bacteriemic phase is followed by sepsis with particular involvement of certain organs. For only thus can we explain the meningitis which had occurred without a previous attack of disease. Surely we must consider meningitis as a manifestation of secondary excitor migration to the meninges.

A special case of lymphogenic dissemination was discovered in the experiments of Asahi et al. These three authors infected goats, rabbits and mice with listeria by contact with small, bloodless lesions of the mouth, the pharyngeal cavity and the conjunctiva. They found that the germs and, with them, the cellular reaction progressed along the nervus trigeminus to the telencephalon. The photograms of cuts through this nerve, which were included in their publication, show that the infection traveled between the nerve fasciculi, i.e. evidently in the perineural lymph spaces. Thus these findings agree with the concept of lymphogenic propagation of listeria.

Bacteriemia persists not longer than 24 hours following single penetration of listeria into the blood, if Osebold and Inouye's findings upon intravenous infection of their experimental animals are also valid for man. However, it must be anticipated that listeria may repeatedly penetrate into the blood stream, once a primary or secondary focus of infection has developed.

The enormous rarity of pronounced listerial sepsis in adults and large animals despite the presence of bacteriemia may be ascribed to a high general resistance. This resistance forms only in the course of the child's development and may break down even at an advanced age. It is missing also in small animals. In all cases of insufficient general resistance we can observe organic metastasis in the form of multiple small granuloma and necrosis as a manifestation of listeric sepsis.

The central nervous system is least resistant to settlement of listeria. Here the excitors are able to establish themselves despite the relatively high general resistance of older children and adults as well as large animals. However, under certain conditions, i.e. during pregnancy, the urogenital tract seems to be considerably more susceptible to listeria. This is indicated by many cases of listeriosis during pregnancy without a sign of meningoencephalitis or even sepsis. In the small animal, too, the urogenital system is especially susceptible to listeria during gestation, but here the mother usually succumbs to sepsis due to her low general resistance. In this connection it should be remembered that pregnancy lowers the resistance not only of the urogenital tract, but, at least in the rodent, also the overall resistance. Potel, Hahnefeld, Gray, Singh and Thorp namely have shown experimentally that listeria doses harmless to nonpregnant guinea pigs and rabbits may cause lethal infections during gestation.

The fetus itself probably is infected exclusively or almost exclusively by passage of germs from the blood stream into the placenta. An infection by aspiration or swallowing of listeria-containing liquor amnii certainly is very rare as a type of primary infection. In this case it must be presupposed that placental foci develop only in the chorionic covering without involvement of the villi, or that the germs ascend through the genital passages and penetrate into the amniotic fluid through the fetal membranes. Such findings are still lacking.

Let us consider how a diaplacental infection of the fetus may come about.

The factor of exposure to infection of the pregnant woman is not dependent on the stage of gestation, which however is the case with the factor of suscep-

tibility for retention of a listeric infection. Here women in the last third of pregnancy are especially disposed. Indeed we find reports of febrile sickness during pregnancy in the anamnesis of women with listeriosis, often cystopyelitis which had occurred several days to weeks prior to birth.

It is certain, however, that the fetus had not been infected at this early stage, but that this happened shortly before its death. This is supported by the fact that typical granuloma of listeriosis, as we find in fetuses and newborn, develop within 1-3 days, and that regenerative forms have never been found in the organs of such children, such as we know of a child that died at the age of 3 months (Hagemann and Simon; Simon) and of animals (Gray and Moore; Linsert).

Therefore some kind of accidental cause must make the fetal infection possible, during the time in which a chronic or intermittent bacteriemia persists in the pregnant woman. Perhaps slight lesions develop in the last months of gestation (mechanically caused by the more vigorous movements of the child and labor) in the villal surface, which in itself is already injured by large fibrinoidal masses.

If, as has been maintained at times, the listeria are able to penetrate the intact epithelium of the chorionic villi, then the fetal infection would take place simultaneously with the occurrence of parental bacteriemia.

The listeria now penetrate the chorionic villi through defects in their epithelium and are carried by the blood into the internal fetal organs. There they multiply enormously due to the absence of general fetal resistance and cause small foci of listeriosis.

The excitors are also excreted into the amniotic fluid with the meconium and urine, enabling the fetus to reinfect itself through aspiration and swallowing.

In connection with the existing fetal sepsis large amounts of listeria also reach the fetal part of the placenta. They also settle there and destroy the villous structure through the vessels. Now the placental foci develop, as described by Hagemann and Simon, Vacek and Benda and recently by Reiss. From these foci the pregnant woman is now massively infected.

This view, which we should like to present for discussion, is supported by the fact that the mother falls violently ill just prior to the abortus and that in every case, also in animal experiments, the mother recovers following expulsion of the fetus. Thus the removal of sepsis foci brings about recovery.

If our assertion is valid, then we can explain further why the fetus is expelled in these moments, regardless of the stage of maturity. It is now that the parental organism is flooded with a sufficiently large amount of abortive listeric toxin. Such a toxin was indicated already in 1952 during Potel's animal experiments, who applied fluid listeria cultures to guinea pigs in advanced pregnancy and noted the abortus of not yet infected young within a few hours. We were unable to demonstrate this effect on the isolated, pregnant or normal uterus of the mouse in vitro. Nor did the smooth intestinal