IMMUNOPATHOLOGICAL CANDITIONS IN CALVES

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A. Immunodeficiency in the newborn calf:

I. Persistent hypogammaglobulinaemia and agammaglobulinaemia.

Calves may die of E. coli septicemia inspite of having received colostrum within the first 24 hrs. after birth. This appears to be a puzzling contradiction. In these calves it has been possible to detect, by immunoelectrophoresis, marked hypogammaglobulinaemia (FEY and MARGADANT, 1961). i.e. in one study 5 of 46 clinically normal calves (10.9%) had hypogammaglobulinaemia. But 21 of 22 calves (95.5%) with E.coli septicemia proved to be hypogammaglobulinaemic or even agammaglobulinaemic. In a later study, the same investigator found a similar incidence: 175 of 191 calves (91.6%) with coli-septicemia proved to be hypo- or agammaglobulinaemic although they had taken in colostrum on the first day after parturition (FEY, 1971). Thus we may consider agammaglobulinaemia an important predisposing factor for coli-septicemia in calves. Since the calf is practically agammaglobulinaemic and becomes normogammaglobulinaemic after the first colostrum feeding, this form should be called " persistent agammaglobulinaemia" (FEY, 1972).

There is some evidence that IgM is the more important immunoglobulin class with respect to coli--septicemia(PENHALE cit. FEY, 1972). In bovine colostrum the O antibodies against pathogenic E. coli strains are predominantly of the IgM variety. Calves severely deficient in IgM invariebly died, although some IgG ($\approx$ 0.8 mg/ml, range: 0.0 - 5.3mg/ml) was present in the serum. Thus, the IgM class of immunoglobulins may be the main component for prophylaxis in the case of coli-septicemia. We should, however, not forget that lethal

cases of coli-septicemia in normogammaglobulinaemic calves have also occurred (MAYR et al.1965).

Pathomechanism of persistent agammaglobulinaemia:

Let us now ask what the possible pathomechanism of persistent agammaglobulinaemia may be. It seems clear that this condition can not be the consequence of the E.coli infection, since cases of hypogammaglobulinaemia have been observed in calves without infection (FEY 1971).- There is no clear relationship between early colostral intake and high gammaglobulin levels in the calf serum and vice versa (FEY and MARGADANT 1962). In other words, in some calves high gammaglobulin levels were obtained after early feeding, in others low levels after early feeding occurred.

Thus, the question of why a newborn calf remains agammaglobulinaemic can still not be answered satisfactorily. It will remain obscure until the problem of the physiological closure of the intestine to immunglobulin absorption between 24-36 hrs. after birth is fully understood.

II- Selective immunoglobulin deficiency:

A selective immunoglobulin deficiency concerning the subclass IgG_2 has been described in adult Danish Red cattle (Nansen, 1974). IgG_2 deficiency was detected in 22 of 312 cattle with various diseases. 13 of 22 had some form of suppurative inflammation. It is, therefore, concluded that bovines with IgG_2 deficiency have descreased resistence against pyogenous infections.

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B. Alteration of the immune response by viral infections:

It has been known for some time that viral infections may alter the immune response of the host. The results of both in vitro and in vivo studies suggest that viral infections can especially depress cellular immunity (HIRSCH et al. 1971; MERIGAN and STEVENS 1971). The result of such depression could then be a state of acquired immunological deficiency.

In man, depression of lymphocyte reactivity has been observed in human newborns with congenital rubella infection (OLSON et al.1967). It was associated with measles (SMITHWICH, and BESKOVICH,1966)and viral hepatitis (MELLA and LANG,1967) . It is also known that animals infected with onocogenic viruses have associated immunological defects; or, many of these viruses show lymphocyte inhibitory capacities.

In the young bovine there is at least one viral infection in which such a pathogenic mechanism may be operative: Bovine Viral Diarrhea (BVD). The BVD virus has an apparent affinity for cells of the immune system. It has long been known that necrotic foci occur in lymph nodes, spleen and Peyer's patches and also a general atrophy of lymphoid tissues. In addition, there are severe leukopenia and anaemia which may persist for several weeks. In vitro studies have provided interesting results which support the hypothesis that BVD virus cause impairment of cellular immunity. One of the in vitro tests to study the function of lymphocytes is the so-called unspecific stimulation of cultured lymphocytes with plant mitogens, i.e. phytohaemagglutinin (PHA). Under stimulation with PHA, normally reactive blood lymphocytes will increase their cellular metabolism (incorporation of tritiated thymidine), will divide and proliferate. The in vitro studies of MUSCOPLAT et al.(1973) revealed that peripheral lymphocytes from calves with BVD infection were unresponsive to stimulation with PHA, meaning that the usual proliferative response

of the lymphocytes could not be induced by the addition of the mitogen to the lymphocyte culture. This observation was confirmed by further in vitro studies: Normal bovine lymphocytes were cultured and then infected with BVD virus. Again, the proliferative response of the lymphocytes to PHA was depressed (i.e. BVD virus depressed the rate of incorporation of tritiated thymidine into lymphocytes). These findings suggest that BVD virus infection in vitro significantly influences the lymphocte response to PHA, that is the ability of lymphocytes to undergo blast transformation. Thus, BVD virus may probably also interfere with the cell's ability to exercise its normal function.

There are a few reports of abnormal immunological phenomean occurring in young bovines infected with BVD virus (McKERCHER et al. 1968). In fatal cases of BVD a complete failure to develop detectable virus-neutralizing antibodies has been observed; even though the animals may have been ill for as long as 11 months (MUSCOPLAT et al. 1973). It is conceivable that this immunological defect is due to the interaction of BVD virus with lymphocytes leading to a temporary deficiency of cellular immunity.

In BVD, changes in the number of B lymphocytes, that is lymphocytes bearing surface immunoglobulins, in the blood have been observed (MUSCOPLAT et al. 1973). While in the normal blood 30% B-cells were present,the blood of two BVD-virus infected calves contained only 4 and 15% B-cells, respectively. Infection of lymphoid cells in the bone marrow with BVD virus was also demonstrated. This corresponds to clinical observations that calves that do survive a congenital BVD infection are usually persistently infected with BVD and have a deficiency in homologous neutralizing antibody (MALMQUIST, (1968).

CORIA and McCURKIN (1978) have described specific immune tolerance in a young bull which was persistently infected with bovine viral diarrhea virus. The infection of this bull had apparently occurred in utero and BVD virus was isolated from white blood cells of the newborn bull calf. Serum-neutralizing antibodies to BVD virus were absent throughout an observation time of 2½ years.

In cases such as this with persistent infection it is not entirely clear whether they represent true immunological tolerance. It is also possible that there is poor antibody production in the newborn calf and that the antibody is complexing with circulating BVD virus to form immune complexes. Evidence for this pathomechanism has been presented by PRAGER and LIESS (1970). They found deposits of immunoglobulin and complement in renal glomeruli, representing components of immune complexes, and in 2/3 of the cases (19/29) also BVD viral antigen.

More generally considered, the immunological defect associated with BVD virus infection may be significant in understanding other virus infections in calves which cause immunological deficiencies and thus predispose for secondary infections with other microbes.

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C. Harmful effects of maternal antibody to the offspring:

Earlier, we have considered those situations where antibody transmitted from the cow to the neonate confers protective immunity. However, in some mammals circumstances may arise in which maternal antibody can have a detrimental effect on the neonate. This is known in the case of haemolytic disease of the newborn or neonatal haemolytic anaemia. In this condition, isoantibody react with red cells in vivo. Haemolytic disease has predominantly been observed in piglets, puppies and foals, but rarely in the bovine species. Pathomechanism: The bovine fetus, by virtue of inheritance from the sire, develops erythrocyte antigens which are not present in the mother. When these cells gain access to the mother's blood stream, they induce antibody formation.If these antibodies are transmitted to the newborn calf via the colostrum, severe haemolytic anaemia is induced.

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Thus,new-born calves become passively sensitized against liver fluke antigen. The sensitization persists for months. By the usual in vivo method, passive cutaneous anaphylaxis, it was shown that these antibodies would indeed sensitize skin by binding to mast cells. In the reaction, the intravenous injection of liver fluke antigen together with a blue dye (Evans Blue) would elicit the typical anaphylactic reaction. In the Prausnitz-kustner-Reaction, performed in three-day-old colostrum deprived calves, the presence of anaphylactic antibodies in the cow's serum was also demonstrated:

1. Intracutaneous injection of the cow's serum followed by
2. Injection of the liver fluke antigen at the same site (Von BENTEN et al. 1976).

Anaphylactic antibodies in reactions against bacterial antigens (PETZOLDT and Von BENTEN, 1978):

Anaphylactic antibodies may be involved in reactions against bacterial antigens. In the studies of Petzoldt calves (60) were vaccinated with an autogeneous vaccine which contained inactivated Staphylococci and Proteus. After revaccination of three-month-old calves six out of 60 showed shock symptoms with severe dyspnoea and three calves died. It was possible to demonstrate in two surviving calves anaphylactic antibody using the direct skin test or by passive sensitization of colostrum-deprived calves(Prausnitz-Kustner-Reaction).

What can we learn from these experiments? In newborn calves, passive sensitization against naturally occurring antigens may occur after intake of colostrum. Since anaphylactic antibodies persist for several months in the skin, the young calf lives in a state of sensitization, and it may be a matter of chance exposure to the same or a similar parasitic antigen that either anaphylactic shock (respiratory symptoms) or protracted anaphylaxis (lesions in the gastrointestinal tract hyperaemia and oedema) occur.

D. Allergy and anaphylaxis in calves:

An evaluation of the pertinent literature reveals that very few reports have appeared which deal with allergic or anaphylactic conditions in claves. This is true for mechanisms which involve anaphylactic antibodies and their pathogenic effect. However, research carried out by two groups in Germany and one in England has shed some light on the occurrence of anaphylactic antibodies in cattle. (HAMMER et al. 1971; EYRE et al. 1973; WELLS and EYRE &970; 1972)and their colostral transmission to calves (MOSSMANN et al. 1974, 1978; Von BENTEN et al. 1976; PETZOLDT and Von BENTEN 1978).

Anaphylactic antibodies predominantly belong to the IgE class of immunoglobulins. There is now good evidence that this type of immunoglobulin occurs in bovine serum (EYRE 1973; HAMMER et al. 1971). One example is the presence of IgE or anaphylactic antibodies against liver fluke antigens in infected cattle (MOSSMANN et al. 1978). More important for this discussion is that IgE has been detected in bovine colostrum and may be transmitted to the newborn calf(HAMMER et al.1971).

Anaphylactic antibodies of the IgE class act in the following way: They are known to bind to mast cells in various organs by way of IgE receptors located on the mast cell membrane, thus sensitising these effector cells. On a second contact with the homologous antigen, mast cells discharge their granule's content: histamine and heparin, which are powerful pharmacological mediators. The consequence may either be a local anaphylactic reaction (i.e.skin) or a systemic, called anaphylactic shock.

Petzoldt and Von BENTEN (1978) have performed experiments to demonstrate the colostral transfer of anaphylactic antibody. In their studies they showed that cows infected with liver fluke (Fasciola hepatica) transmit anaphylactic antibody to the neonate by way of colostrum. The antibody concentration in the colostrum may be 10 to 20 times greater than in the serum.

Other allergic conditions that are know in adult cattle have not been observed in young calves, i.e. allergic pulmonary disease (synonymously called pulmonary emphysema, atypical interstitial pneumonia or fog fever). This disease occurs in cattle on pastures in late summer and autumn (ROBERTS et al. 1973). There is evidence that actinomycetes such as Thermopolyspora polyspora is the antigen.

Allergic reactions occurring after foot and mouth vaccinations have also not been observed in young calves. These reactions are most likely due to complexes of FMD-virus and antigens (lipoprotein) in BHK-cells. According to other investigators sensitization may be due to other substances in FMD-vaccines, i.e. formalin denatures bovine serum, carboxymethyl-cellulose and antibiotics.

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E. Thymic hypoplasia and parakeratosis in calves:

The lethal trait A 46 has been described in calves of the Black Pied Danish Cattle of Friesian descent. The clinical picture is characterized by parakeratosis. An interesting feature is the premature involution of the thymus. While affected calves seem to have a normal-sized thymus at birth and in the first three weeks of life, diseased calves may have marked thymus hypoplasia, associated with depletion of peripheral lymphoid tissues. Danish workers have clearly shown, in immunological investigations, that diseased calves have an impairment of their cell-mediated immune response. Skin testing in affected calves revealed a very poor primary response to test antigens such as dinitrochlorobenzene and Mycobacterium tuberculosis antigen. A slight decrease in the humoral immune response was also observed. As a working hypothesis it is suggested that zinc-ions are important for the normal development of the thymus.

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