The fetal and neonatal animals are special

Fetal and neonatal animals are not “mini-adults.” So it is unrealistic to expect them to have the same range of diseases as older animals, and have the same type of responses to injury. Some of this is obvious, particularly during organogenesis when teratogenic compounds and infectious agents wreak havoc, with little or no effect on the dam. This winter the WSVL has seen this in a graphic way: recurrent abortion due to off-label use of bovine herpesvirus-1 vaccine (BoHV-1). The virus in this line of products is attenuated so that it has essentially no clinical effect on immunologically competent post-natal cattle. It is designed to be given to pregnant cattle, since field strains of BoHV-1 are abortifacient. But it should be given to pregnant animals provided they were vaccinated pre-breeding. When producers forget to give one or more pre-breeding shots, and vaccinate pregnant cattle, a proportion of the cattle abort. Indeed, under circumstances we don’t fully understand, particularly when well vaccinated pregnant cattle are vaccinated, some still abort. We had several such episodes in 2010 and 2011. For the same reason, some of the infectious agents that are minimally pathogenic in immunologically competent animals – such as Toxoplasma gondii – can cause fetal death and abortion.

The peculiar vulnerabilities of animals in utero

In this lecture I list several of the ways in which the fetus differs from post-natal animal. The two most obvious are immature immune system, and development of tissues and organs during organogenesis. Both create special targets and unique lesions, particularly when infectious agents cross the placenta. The development of the immune system establishes some distinctive disease syndromes, such as with pestiviruses (bovine viral diarrhea virus; border disease virus). If animals are infected before the immune system in fetal cattle (BVDV) and sheep (BDV) is competent, the pestivirus is recognized as “self” and results in persistent infection, with virus present in essentially all tissues. This may cause abortion, or result in the birth of animals that harbor and shed the virus for life, short though that may be. As a general rule, the fetus is far more susceptible to infection that post-natal animals. Infectious agents that are typically only seen as disease-causing factors in immunosuppressed post-natal animals are a common cause of severe or fatal disease in animals in utero. Damage to tissues during organogenesis, if it does not cause abortion, is responsible to the varying effects of infectious agents at different stages of gestation. In the lecture I show a slide that illustrates critical periods of development during human organogenesis. The embryonic period (especially between 3 – 8 weeks in humans) is a particularly vulnerable period, as this is when organs are formed. The periods of vulnerability vary for each organ system. The brain, since it continues to develop until after birth, remains susceptible to injury throughout gestation. By contrast, other organs or tissues have shorter periods in which teratogenic injury can be induced. Another peculiarity of the fetus is its dependence on a temporary organ, the placenta, for nutrition, oxygenation and disposal of metabolic wastes. Injury to the placenta results in compromised development or abortion. Some infectious agents that tend to target the
placenta with little or no invasion of the fetus, or at least no recognizable fetal lesions. One such, *Coxiella burnetti* (the Q fever agent), is rarely found in fetus following infection of the dam, yet is present in extraordinary numbers in placental trophoblasts. Presumably, the high rate of “lesionless” fetuses we see in aborted calves (60% of all seen in the necropsy room), sheep (60%), and foals (40%) reflects agents that damage the placenta and/or fetus without causing recognizable lesions. Almost certainly this includes some novel infectious agents. Other unique features of the fetus are its existence in a sterile environment, organ-specific features such as blood flow (bypassing the lungs in utero), temporary anatomical features (such as urination into the amniotic sac; ductus arteriosus), and susceptibility to the metabolic crises in the dam.

**Fetal anomalies**

A congenital anomaly (present at birth) does not mean it is genetic (due to a genetic defect), although many are. Many congenital anomalies, particularly in food and companion animals, are due to infectious and toxic exposures in utero. And some genetic defects may not be manifest until after an animal is born. Many inherited storage diseases (please see Dr. Montgomery’s lecture) do not develop until adolescence. There are some genetic diseases that do develop until late in life. One such, Huntington’s disease, which is Dr. Fox’s research area, is inherited as a dominant inherited trait and does not occur until 4th or 5th decade of life. This is one of a family of diseases that long puzzled geneticists, who did not have a good explanation for why this familial disease appeared to become worse in subsequent generations. The explanation is that it due to trinucleotide-repeat mutations (below). In animals there are several genetic diseases that do not occur until later in life. Many of the inherited blinding disorders of dogs that affect retinal photoreceptors (rods and cones) do not occur until they are adolescent or mature – hence, the confusing distinction between inherited photoreceptor dysplasias, affecting dogs (e.g., Irish setters) as photoreceptors develop after birth, and those that occur later in life, called inherited photoreceptor degenerations, once photoreceptors are mature. These may not cause blindness until a dog is 5 – 7 years old.

An estimated 1 in 33 children born in the United States comes into the world with a birth defect. Such defects are the most common cause of death in the first year of life, and an appreciable cause of morbidity and mortality in subsequent years. I am not aware of comparable estimates for animals, but some 20% of all fertilized human ova are anomalous and fail to develop. Other fertilized ova have less severe defects, and are compatible with limited fetal development. These are the basis for “spontaneous” abortions – which in truth are the result of abnormal development, most often due to chromosomal anomalies. The basis for a high proportion (40 – 60%) of congenital human defects is unknown. Of the remainder, genetic defects account for 12 – 25%, multifactorial account for 20 – 25%, infectious account for 2 – 3%, drugs and chemicals for 1%, and material diseases for 6 – 8%. In domestic animals there are few comprehensive studies of the causes of abortion and perinatal death. Such studies tend to be weighted toward studies of infectious agents and focus on the latter part of pregnancy when a fetus is likely to be found by owners rather than coyotes. Based on published numbers, infectious and toxic causes are more important as causes of reproductive wastage than in
people, and chromosomal anomalies less important. There is one caveat: there is a dearth of studies of the incidence of chromosomal anomalies in congenitally defective animals.

**Genetic defects**

The most important genetic defects found birth are due to chromosomal abnormalities or mutations in single genes that have large effects. The latter follow Medelian inheritance. The three major classes are autosomal recessive, autosomal dominant and sex-linked traits. In class I showed slide of the relative frequency of human autosomal, sex-linked and mitochondrial diseases. The first class of diseases number is in the 1,000s, the second are in 100,s, and third are in the 10s. Definition of these diseases has grown enormously in the past decade, due to the advent of molecular diagnostic tools. Prior to this, characterization depended on recognizing abnormal gene products, or their clinical effects. The commercial availability of single nucleotide polymorphism-chips (SNP-chips) greatly accelerated this process. It has allowed screening of cohorts of individuals with a defined suspect genetic disorder, and comparison to individuals without the trait. SNP-chips are increasingly used in animals to define economically important diseases, but we are still a long way behind human medicine in terms of the range of diseases characterized by a defined mutation.

a) **Mendelian disorders.** Single gene disorders are most easy to understand due to the one gene-one protein-one disease connection. They may result in defective enzymes (such as lysosomal storage diseases), loss of enzyme inhibitors (α1-antitrypsin, which normally inhibits tissues proteases such as elastase; it is one major cause of pulmonary emphysema), loss of receptors (such as low density lipoprotein receptors, leading to familial hypercholesterolemia), loss of transporter proteins (such as for ions, leading to cystic fibrosis), or structural proteins (either in extracellular matrix or in cell membranes). **Familial hypercholesterolemia** is one of the most common Mendelian disorders. Affected individuals lack a receptor for low density lipoproteins, leading to loss feedback control and a high risk of atherosclerosis and cardiac infarction. What complicates our understanding of the clinical disease is the large number of mutations involving the LDL receptor: more than 900. These are classified by the site at which the effect of the mutation is manifest, whether during synthesis, transport, binding, clustering or recycling of the receptor from endosomes. Similarly, **cystic fibrosis** is a common disease in children. Some >1300 mutations have been reported in the cystic fibrosis transmembrane conductance regulator gene (CFTR). The CFTR protein regulates multiple ion channels. In normal individuals its presence allows chloride secretion into the lumen of respiratory and digestive tracts. When the CFTR protein is defective, chloride cannot be secreted and water content on epithelial surfaces is reduced. The end result is abnormally thick viscid surface mucus, predisposing affected children to respiratory infections. Not all defective CFTR channels are created equal. Some mutations result in a complete absence of channels (defective protein synthesis or processing, or inability to interact with ATP), leading to classical cystic fibrosis. Others result in less functional channels, or reduced abundance, resulting in milder forms of the disease.

b) **Chromosomal disorders.** According to some estimates about 1 in 100 children is born with a detectable chromosomal abnormality. A high proportion of miscarriages early in gestation are due to
chromosomal defects. The simplest form of chromosomal disorders involve having one too many or one too few chromosomes. Loss of one of the autosomes is not compatible with life, and generally results in resorption or miscarriage. Acquisition of an additional chromosome, such as in trisomy 21 (Down syndrome), can be compatible with life, but at a price. Down syndrome children are mentally retarded, at higher risk for leukemia and infection, and develop Alzheimer’s disease at an early age. Other chromosomal disorders involve various chromosomal rearrangements, such as translocations (segment from one chromosome transferred to another), inversions (segments of chromosome are inverted), and deletions.

C) Single-gene disorders with non-classical inheritance. This is a set of genetic disorders caused by trinucleotide repeat expansion, resulting in trinucleotide repeats in certain genes that exceed the normal stable threshold for that gene. If the repeat is present in a healthy gene, a dynamic mutation may increase the repeat count and result in a defective gene. This group of disorders, which was first recognized in 1991, is with some exceptions characterized by autosomal dominant inheritance, midlife onset, a progressive clinical course, and a correlation of the number of CAG repeats with the severity of disease and age at onset. Family studies suggest that these diseases are associated with ‘anticipation’: the tendency for progressively earlier or more severe expression of disease in successive generations. The example of this disease I gave in class was Huntington’s. Mutation in the Huntingtin gene codes for a toxic form of the protein, resulting in neuronal damage in selective areas of the brain.

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