PHYSIOLOGICAL LIMITS TO REPRODUCTION
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SUMMARY
Major physiological factors affecting reproduction are those affecting the number of ova ovulated and fertilized, rate of embryonic survival, physical and biochemical components of uterine capacity, fetal/placental development and survival to term, as well as survival of the neonate as influenced by birthweight and maternal behavior of the dam. Ovulation rate can be increased nutritionally by increasing energy intake, by injection of exogenous gonadotropins during the preovulatory period and through genetic selection. Fertilization rates generally exceed 90 to 95% and are not considered as limiting to increasing reproductive efficiency. Embryonic death losses claim 25 to 50% of potential offspring and represent a major deterrent to improving reproductive efficiency in livestock. Interactions between the conceptus (embryo and its associated membranes) and maternal system are essential for establishment and maintenance of pregnancy. In livestock, these signals, in general, insure maintenance of the corpora lutea (CL) and production of progesterone, as well as stimulate uterine functions which insure delivery of adequate nutrients to the conceptus in the form of histotroph (epithelial secretions) and hematotroph (exchange of nutrients between the maternal and embryonic/fetal circulations). Autocrine, paracrine and endocrine factors affect growth and development of the embryo/fetus and placenta and these may be influenced by genotype of sire, dam and/or fetus. Hormones of the fetal/placental unit and maternal system interact to stimulate mammogenesis and lactogenesis to insure a source of nutrition necessary for survival of the neonate. These physiological limitations to increasing reproductive efficiency of livestock will be discussed and, where possible, differences between prolific and nonprolific breeds will be noted.

INTRODUCTION
It is apparent that physiological limits to increasing reproductive efficiency involve multiple interactions between organs and tissues of the maternal system and those of the conceptus. Increases in reproductive efficiency of livestock during this century have been realized because of improved nutrition and management practices resulting in some increases in prolificacy, but primarily as a result of increased frequency of farrowing, lambing, calving and foaling. Since most emphasis in reproduction in horses is on advancing the breeding season and decreasing embryonic/fetal death losses and not on increasing frequency of foaling or the incidence of twins, this paper will focus on results from studies of cattle, sheep and swine. Regardless of species of livestock, reproductive rates are regulated by number of ova ovulated and fertilized, rate of embryonic/fetal survival and rate of neonatal survival. Researchers have considered the feasibility of increasing prolificacy in cattle, primarily through the induction of
twinning, but there are no breeds of cattle with sufficiently high rates of twinning to allow one to define the physiological and endocrinological traits associated with higher rates of prolificacy in cattle. In sheep and pigs, however, prolific breeds are now being studied to identify and define determinants of prolificacy. Comparison of prolific and nonprolific breeds of sheep and pigs should also allow scientists to define the physiological limits to reproduction and identify genetic regulation of those processes. It is of interest to note that prolific breeds of sheep (Romanov and Finnish Landrace), but not prolific breeds of pigs (Chinese Meishan), have higher ovulation rates. In addition, mammary gland function has not been defined for prolific breeds of sheep, but prolific Chinese Meishan pigs have more mammary glands than conventional breeds of swine.

DISCUSSION

Cattle. At present, there seems to be little interest in increasing prolificacy or twinning in cattle. In dairy cattle, twinning is associated with increased frequency of retained placentae and reduced lactational performance, both of which are undesirable. Extensive management of beef cattle dictates that each cow produce, each year, a single healthy calf that has a high probability of survival to weaning. Limitations to increasing prolificacy in cattle are due to management and not necessarily to physiological limitations (see Seidel, 1981).

Physiological limitations to increasing reproductive performance in cattle include ovulation rates that are generally one per oestrous period, variable rates of fertilization of ova (70 to 95%), failure of intrauterine migration and spacing of embryos to enhance embryonic/fetal survival, high rates of embryonic death and relatively high rates of fetal deaths when multiple fetal-placental units are present in the same uterine horn. For cows that do produce twins, maternal behavior and milk production become limiting since cows tend to abandon one calf under extensive management conditions. Milk production by many beef breeds is inadequate to support an acceptable rate of growth and survival of more than one calf to weaning.

Embryo transfer in cattle is the most effective means for increasing the frequency of twinning in cows. It has been shown that reproductive performance is poor following the use of gonadotropins to superovulate cows. Using embryo transfer, one embryo can be deposited in each uterine horn in an attempt to insure that adverse effects of intrauterine crowding are minimized. Maternal limitations associated with uterine capacity to support adequate fetal-placental development to term and growth of the neonate cannot be studied effectively until routinely successful methods for inducing twinning are available.

Sheep. Results of studies of Booroola Merino, Finnish Landrace, Romanov and other prolific breeds of sheep suggest that ovulation rate is the primary physiological limitation to increasing prolificacy. The following discussion is based primarily on results reported by Bindon & Piper (1986a). Booroola Merino ewes are currently classified as F/F, F/+ and +/+ when ovulation rates are greater than 5, 3-5 and less than 3, respectively, since more precise methods are not available. Mean ovulation rates for Booroola Merino ewes in one study were 4.2 (range from 1 to 11) and litter size from the same ewes averaged 2.5 born, with a range from 1 to 7. Control Merinos having ovulation rates of 1, 2 and 3 give birth to 76, 112 and 90 live lambs/100 ewes lambing. Lamb survival rates were 88 and 79% for singles and twins resulting in 67 and 88 lambs weaned/100 ewes. For Booroola Merino ewes having 1, 2, 3, 4, 5 and 6 ovulations, lambs born and weaned/100 ewes were
89 and 80, 152 and 117, 189 and 104, 128 and 41, 130 and 39, 150 and 32, respectively. The marked difference between lambs born and lambs weaned was due to the fact that lamb survival was similar to that for Control Merinos for singles (90%) and twins (77%), but then declined to 55, 37, 30 and 28% for ewes giving birth to 3, 4, 5 and 6 lambs. In that study, increased efficiency of reproduction and production of Booroola Merino ewes was not realized when ewes ovulated more than three ova and/or gave birth to more than three lambs.

Transfer of three embryos to Booroola or Control Merino ewes resulted in an average of 2.6 and 2.4 lambs born per ewe, respectively (Bindon and Piper, 1986b). These results differ somewhat from those cited above from Bindon et al. (1986a). In that study, Control Merino ewes having ovulation rates of 1, 2 and 3 had 0.76, 0.56 and 0.30 lambs born per corpus luteum, whereas Booroola Merino ewes with 1, 2, 3, and 4 ovulations gave birth to 0.89, 0.76, 0.63 and 0.32 lambs/ovulation. These results suggest that a major increase in embryonic/fetal death occurred in control ewes when ovulation rate exceeded two, but did not increase to a similar level in Booroola ewes until ovulation rate exceeded three. Nevertheless, the previous statement that ovulation rate is the major physiological limitation to increasing reproductive efficiency seems to be true so long as ovulation rate does not exceed three. When it does, low survival rates for lambs results in a negative effect on reproductive efficiency. This suggests that factors affecting intrauterine growth of the fetal-placental units, lactational performance of ewes and/or failure of ewes to express strong maternal traits essential for lamb survival become limiting.

Researchers have not adequately studied the unique ewe that can give birth to strong sets of triplets or quadruplets and wean a high percentage of those lambs. It would be interesting to determine if the uterine vascular architecture of those ewes allows for minimal resistance to increasing uterine blood flow and substrate delivery and if the ability of the maternal heart to perform work is greater for the highly prolific ewe. If so, are those traits heritable? It is of interest to determine if increased prolificacy in Booroola Merino ewes associated with the single F gene mutation affecting ovulation rate and the genetic basis for increased prolificacy of Romanov and Finnsheep are comparable. The question is whether there is increased uterine capacity and superior maternal traits in Romanov and Finnsheep which evolved as prolific breeds, presumably through selection, over a much longer time period than the Booroola Merino. Data are not available to indicate differences in lamb survival and maternal traits between Booroola Merino, Finnsheep and Romanov in the same environment.

Swine. Ovulation rates in swine are potentially limiting to reproductive performance, but this can be overcome through increasing energy intake during late dioestrus and prooestrus, injection of exogenous gonadotropins and by genetic selection (see Wrathall, 1971). Fertilization rates in swine are 95% or greater and, therefore, are not a physiological limitation to reproduction. Embryonic death losses in pigs have been estimated to reduce potential litter size by 25 to 50% in conventional breeds of swine. When ovulation rates are in the normal range and endometrial surface area has not been experimentally limited by performing unilateral ovariectomy-hysterectomy, about two-thirds of the embryonic death losses occur between Days 8 and 12 of gestation. This is a critical time in development of pig conceptuses as they make the transition from spherical to tubular to filamentous morphological forms, initiate secretion of oestrogens required for establishment of pregnancy and begin to form intimate contact with the uterine endometrium as placentation is initiated. When litter size
is exceptionally high early in gestation, e.g., following superovulation, there is considerable fetal death loss between Days 50 and 70 of gestation such that litter size at term averages only 0.5 to 1.0 more piglets than control gilts and sows (see Bazer & First, 1983).

Uterine capacity in swine refers to physical aspects of endometrial surface area and the potential of endometrial tissue to provide nutritional support for conceptus development. The latter includes secretory activity of endometrial epithelium and epithelial transport mechanisms for movement of substrate, e.g., glucose, into the uterine lumen. Also required are potential for high rates of uterine blood flow and hematotrophic exchange of nutrients and gases, interactions between endometrium and conceptuses essential for their growth and differentiation, as well as biochemical signalling for establishment and maintenance of pregnancy. Each conceptus interacts only with that endometrium with which it is in contact and survival of each conceptus is dependent upon the efficiency of placentation, i.e., did it occur at the proper time and were the appropriate biochemical and molecular signals from the conceptus sent and received in adequate amounts at the proper time. Biochemical and molecular probes available to assess efficiency of conceptus-endometrial interactions provide powerful tools to evaluate this physiological limitation to reproductive efficiency. The fact that individual pig conceptuses die without loss of the entire litter underscores the importance of local interactions between uterine endometrium and conceptus.

Deaths of individual conceptuses within a uterine environment account undesirable reductions in litter size; therefore, it seems appropriate to understand conceptus-endometrial interactions and not consider uterine or conceptus functions independently. There is a caveat to this discussion. It is possible that a high percentage of ova ovulated are either immature or contain genetic defects. Koenig et al. (1986) detected more immature ova when gilts were hormonally superovulated (15.7 vs 8.2% for control gilts) or from genetic lines selected for high ovulation rates (14.4 vs 8.5% for control line gilts). Percentage of ova with chromosomal abnormalities averaged about 25% regardless of whether gilts were superovulated, select line gilts or control gilts. If percentages of these two defects of ova are combined, they could account for 33 to 42% of ova ovulated; figures not too different from available estimates of embryonic death losses in swine. These results are potentially very significant. Koenig et al. (1986) studied ova collected from the oviducts 8 to 32 h post-ovulation. Previous estimates of genetic defects may have been artificially low because estimates were made from blastocysts collected after loss of abnormal embryos had occurred. If a high percentage of embryonic death losses do result from fertilization of meiotically immature ova or ova with chromosomal defects, high rates of embryonic mortality in swine may be predestined to prevent further development of zygotes with genetic defects. The potential for eliminating this physiological limitation to reproduction has been given very little attention.

Recent reports have indicated that gilts that ovulate uniformly during a short period of time have conceptuses on Day 11 that are more uniform (Pope et al., 1988). The presence of both small and large conceptuses in the same litter results in death of the small conceptuses; however, when transferred alone to a less developed uterine environment, small conceptuses are viable (Pope, 1988). At present, the frequency of losses of small conceptuses resulting from fertilization of ova ovulated late in the ovulatory process has not been established.

Prolific Chinese Meishan pigs are now being studied in France, Great
Britian, West Germany, The Netherlands, Japan, the United States of America and China to understand determinants of prolificacy. Knowledge gained from studies of Meishan pigs will impact our understanding of reproduction and lactation since their mammary line and maternal behavior both appear superior to our conventional breeds of swine. The People's Republic of China has a history of domestication of pigs dating back 6000 to 7000 years and possibly 10000 years (Peilieu, 1984). In the lower Changjiang River Basin three types of pigs within the Taihu breed are exceptionally prolific, attain sexual maturity at an early age and have 16 to 20 mammary glands. In November 1979, the government of France imported, for experimental purposes, three breeding pigs, 2 females and 1 male, of each of the Meishan, Jiaxing and Jinhua breeds from the People's Republic of China. Bidanel & Legault (1986) and Bolet et al. (1986) reported results of extensive breeding studies in which they compared reproductive traits of two breeds of pigs commonly used in France, the Large White and French Landrace, with the Meishan, Jiaxing and Jinhua breeds. Females of the Meishan breed were highly prolific compared to females of the Large White breed, due to low rates of embryonic mortality for Meishan gilts and sows and not to differences in ovulation rate. Identification and study of prolific breeds of pigs is important scientifically since estimates of litter size has changed very little since Sir John Hammond (1914, 1921) first established the relationship between ovulation rate and litter size and determined that embryonic-fetal death losses claim 25 to 50% of potential offspring in breeds of pigs commonly used for meat production. In the intervening years, genetic selection within breeds and utilization of cross-breeding systems have resulted in increases of only 1-1.5 piglets born per litter (see Legault, 1985).

Bidanel & Legault (1986) reported that the advantage in litter size born to F1 females from cross-breeding Meishan and Large White breeds (15.3 piglets) over that of Large White sows (10.7 piglets) was greater than that of females obtained from crossing hyperprolific Large White sows and Meishan boars (17.4 piglets) over that of hyperprolific Large White sows (13.1 piglets). These advantages in litter size for Meishan females was due to low rates of embryonic deaths which may be due to faster and/or more uniform development of embryos with genetic contributions from Meishan sows or boars. Goldbard & Warner (1982) detected an H-2 associated gene (preimplantation embryonic development, Ped gene) in mice which determines whether mouse embryos have fast, normal or slow rates of development during the preimplantation period. More recently, Warner et al. (1986) reported MHC antigens of the SLA complex on pig embryos (Days 2 to 6), indicating that a search for a pig Ped gene is warranted.

Meishan gilts reach puberty earlier (91 ± 2 vs 192 ± 3 days), have longer periods of oestrus (60 ± 2 vs 49 ± 2 h) and shorter interoestrous intervals (19.1 ± 0.2 vs 19.8 ± 0.2 days) than Large White gilts (Bazer et al., 1988a). Uterine length, uterine weight, width of uterine horns, endometrial surface area, endometrial weight and percentage of uterine weight represented by endometrium are greater for Large White than Meishan gilts. However, breed differences were not significant when slaughter weight was included as a covariate in the analyses, indicating that development of the reproductive tract was proportional to body weight for each breed. These results indicate that the more prolific Meishan gilts: (1) reach puberty at an earlier age and lighter body weight; (2) express oestrus longer, but have shorter oestrous cycles and (3) have smaller uteri. In addition, ovulation rate tended to be higher for Large White gilts, suggesting that this trait is not a primary determinant of prolificacy favouring Meishan gilts.

Results from a related study (Bazer et al., 1988b) indicated that
conceptuses of Meishan gilts develop more rapidly and more uniformly between Days 8 and 14 of gestation than conceptuses from Large White gilts. Overall, embryonic survival for Days 8 to 12 for gilts not having elongated conceptuses was 90.2% for Meishan and 73.2% for Large White gilts. On Day 30 of gestation, embryonic survival was also higher for Meishan (89%) than Large White (55%) gilts. However, embryonic weight, crown-rump length, placental length, allantoic fluid volume, amniotic fluid volume, as well as total glucose, fructose and protein in allantoic fluid were not affected by breed. Placental weights were greater for Large White gilts. Uterine development at Day 30 of gestation, based on total length and weight of uterine horns, width of uterine horns, total endometrial surface area and total endometrial weight was greater for Large White gilts. Ovulation rates, measured as the number of CL, on Days 8 to 14 and on Day 30 were higher for Large White gilts. These results indicate that: (1) ovulation rates were lower and uteri were smaller for prolific Meishan gilts; (2) conceptus development was faster and more uniform between Days 8 and 14 of gestation for Meishan gilts was associated with higher embryonic survival; and (3) embryos and placentae surviving to Day 30 had similar weights and lengths, but embryonic survival to Day 30 of gestation was higher for Meishan gilts. Factors regulating rate and uniformity of conceptus development in swine may be primary determinants of prolificacy.

Selected components of uterine secretions collected from Large White and prolific Chinese Meishan gilts during the oestrous cycle and early pregnancy have also been studied (F.W. Bazer, W.W. Thatcher, F. Martinat-Botte, M. Terqui, S. Bernard, J. Raveau and M.C. Lacroix, unpublished results). The uterine secretions were assayed for: (1) total protein, an overall index of secretory activity by tissues; (2) uteroferrin, a measure of secretion of a progesterone-induced protein; (3) acyl aminopeptidase, a marker enzyme associated with membrane processing during endocytosis and exocytosis by endometrial and/or conceptus tissues; (4) calcium, released from the endometrium in response to oestrogens secreted by conceptuses; (5) oestradiol 17-β, the conceptus signal associated with establishment of pregnancy and initiation of endometrial secretory activity; (6) glucose, a substrate transported into the uterine lumen and converted to fructose by the trophoectoderm; (7) immunoglobulins A and G, molecules selectively and passively, respectively, transported into the uterine lumen in response to effects of conceptus oestrogens which result in recruitment of plasma cells into the endometrial stroma and (8) prostaglandins (PG) P2 and PGE, products of endometrium and conceptuses that exert local influences on the intrauterine environment. For each of these measures of conceptus-endometrial interactions affecting the accumulation of histotroph in the uterine lumen, the Meishan uterus was more efficient; the only exception being uteroferrin. In addition, insulin-like growth factor-I is present in higher amounts in uterine flushings of Meishan than Large White gilts (Simmen et al., 1989). These differences in conceptus-endometrial interaction favoring Meishan gilts may also be determinants of prolificacy.

Concentrations of total unconjugated oestrogens and progesterone in plasma were not different between Large White and Meishan gilts, but concentrations of prolactin in plasma were higher for both cyclic and pregnant Meishan gilts. These findings suggest that differences in peripheral levels of oestrogen and progesterone do not account for the higher uterine secretory activity of pregnant Meishan gilts. Rather, Meishan conceptuses may produce factors which have a greater stimulatory effect on the uterine endometrium or the Meishan endometrium may be more sensitive to conceptus signals which stimulate uterine secretory activity. It is also
possible that higher concentrations of prolactin in serum of the Meishan gilts increase endometrial sensitivity to conceptus signals or affect transcriptional or translational events affecting the releasable pool of proteins that endometrial epithelial cells secrete (Young et al., 1989). Since pig conceptuses have a noninvasive implantation, secretions from endometrial epithelium are essential for conceptus development for most, if not all, of pregnancy.

REFERENCES