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Reproductive challenges facing the cattle industry at the beginning of the 21^{st} century

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The aim of this review is to pinpoint the areas that require further research for greatest impact to improve the efficiency of dairy and beef production. Increased knowledge about the principal causes of reduced fertility is essential. Increases in milk yield have been at the expense of reduced fertility in dairy cows and although diet has a major impact, the precise interaction between nutrition and reproduction still needs to be characterized in both beef and dairy cows. Furthermore, during periods of inadequate nutrition or stress, the intensity of oestrus is reduced by inadequate exposure to oestradiol. However, it is still unclear which pheromones are involved at oestrus, how synthesis is controlled and how pheromones are detected in herd-mates. GnRH may be involved in behaviour but the brain centres that translate hormonal messages are unknown. Attempts to overcome poor oestrous detection include measurements of milk progesterone, telemetric pressure detectors and devices that record the extra activity at oestrus. Substitution of heat detection by 'hormone treatment remedies' has met strong consumer resistance in Europe. The creation of larger cattle units and increased movements world-wide render herds more susceptible to infectious agents, such as *Neospora, Leptospira, Trypanosoma* and Bovine Viral Diarrhoea virus (BVDv), but it is unclear how other clinical conditions, such as lameness or endometritis, also interfere with ovarian function. The future of dominant follicles selected within 14 days after parturition is crucial – normal ovulation, prolonged persistence or atresia. Calving carries the greatest risk in the reproductive life of a cow and yet little work has focused on reducing the frequency of this event. For dairy cows, a greater understanding about induced or extended lactation is required. For beef animals, precise induction of twinning and nutritional adjustments could produce two offspring per pregnancy. At the start of pregnancy, the trophoblast produces interferon to prevent luteolysis, but the immunological implications are unknown and it is not clear how the rest of pregnancy is maintained. Profiles of

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pregnancy specific protein B (PSPB) have increased understanding of embryonic death. However, 25% of cows in abattoirs are pregnant, even though 30% of involuntary cullings are 'for failing to conceive'. Clearly, this is an area of wastage that requires urgent resolution. It is unknown why undernutrition at the time of insemination or in early pregnancy leads to delayed births, low fetal weights and later adverse health. At the end of pregnancy, the fetus controls the onset of parturition, but very little is known about the biochemical control of cervical dilation and placental separation. On the male side, bulls are selected for optimal freezability of semen; however, there is as yet no reliable predictor for semen fertility. Methods for accurately pre-determining the sex of both semen and embryos will revolutionize the dairy and beef industries.

Introduction

The aim of this review is not to cite all research to date on fertility of cattle, but rather to pinpoint the gaps that deserve early attention for greatest impact on progress to improve the efficiency of the dairy and beef industries. Inevitably, more questions will be raised than answered. With the need for increased agricultural efficiency, there has been greater adoption of intensive management practices but in future these will have to be balanced against welfare considerations and public opinion.

Some reports suggest a link between marked increases in milk yield and a 1% reduction per year in conception rates to the first insemination after parturition over the past 20 years, whereas other reports claim that no such association occurs (Lucy, 2001). Nevertheless, there has been a proposal that the effects on fertility have a genetic origin (Royal *et al.*, 2002). This proposal must be reconciled with continued good fertility of nulliparous heifers, although it is possible that there is an underlying genetic basis that is only revealed when the dairy cow is put under the pressure of high lactation yields. Indeed, a new genetic index for longevity (production lifetime) incorporates body condition score as one of the integral measurements required to improve the precision of selection indices or criteria (Pryce *et al.*, 2001). This also raises the issue of the correct definition or indices to be used to define efficiency. Which is the most important index to use? Should it be the number of inseminations per pregnancy, the lifetime of profitable production or more probably the input (dietary energy/protein and cow years) required per litre of milk or kilogram of beef meat? Even methods used to evaluate fertility of cattle herds are not agreed across the world. Recently, it has been suggested that to monitor fertility in year-round calving herds, 100-day in-calf rates and 200-day not-in-calf rates are valuable, in addition to the traditional parameters (www.drdc.com.au). Whatever the methods used to evaluate fertility records, there is also a requirement for accuracy so that specialist advisers and computer software can meaningfully interpret the information with farmers.

Few breeds of cattle produce first offspring at less than 2 years of age, owing to the timing of puberty and the increased incidence of dystocia in very young heifers. Thus, long generation intervals pose a challenge for both geneticists and reproductive biologists. For reducing generation intervals, there is considerable interest in obtaining gametes from prepubertal animals with the inherent need for further development of *in vitro* techniques (de Paz *et al.*, 2001). Indeed, the development of these new reproductive technologies has highlighted our lack of understanding of oocyte and zygote biology and this requires urgent attention.

Throughout the world, different breeds of cattle thrive on diverse feedstuffs, thus making best use of available nutrients. Depending on the prevailing supply, farmers can either choose low input, low output systems, such as the 'milk-from-grass' approach in New Zealand, Australia and Ireland, or high input, high output systems on farms that rely on high density foods as exemplified by soya and maize systems in the UK, USA and the Netherlands. For both of these systems, farmers take high-risk strategies to maximise economic returns and even minor deviations to these delicate balancing acts can have major consequences. In the face of declining fertility, it is imperative to identify the most sensitive links in the mechanisms controlling reproduction. Indeed, a greater appreciation of all factors that interfere with the equilibrium regulating reproduction is required. Lessons can be learned by appreciating factors affecting cattle reproduction throughout the world, for example, there are indigenous breeds of *Bos taurus* or *indicus* (zebu) that can digest more ligneous forage and have the added advantage of greater resistance to region-specific diseases, such as trypanosomiasis, babesiosis or theileriosis. However, relatively little is known about the precise factors that govern the success of fertility in all of these situations.

Influence of the environment

There is increasing evidence that endocrine disruptors such as pesticides influence cattle fertility (Jacobs and Lewis, 2002). These compounds are being identified but exactly how are the effects mediated, and what are the precise indicators of the most deleterious compounds?

Another important environmental factor concerns poor farm design and housing. In large herds with access to pasture it is quite probable that cattle will have to walk or roam considerable distances in less than ideal conditions. This diverts dietary energy away from milk or meat production leaving the animals deficient in essential nutrients. In addition, if an animal has to spend a considerable part of the day searching for food, behavioural time-budgets will be altered resulting in fewer opportunities for expression of oestrus (Singh *et al.*, 1993). Furthermore, long walks will predispose animals to lameness which, in turn, has deleterious effects on fertility (Collick *et al.*, 1989). When housed inside, an appropriate environment must be provided – simple aspects include non-slippery floors for confident expression of oestrus, sufficient head-space at feed barriers and appropriate group sizes to enable correct functioning of hierarchies (Vailes and Britt, 1990; Dobson and Smith, 1998).

If lactating cows are kept outside, they are exposed to weather conditions – lower critical temperatures without wetting are not usually a problem, but heat stress can result in considerable long-term difficulties. One novel solution has been to remove the affected oocytes from all antral follicles in the ovary using ultrasonography per vaginam (Wolfenson *et al.*, 2000). Thus, the short-term influence of heat stress can be averted; whether this approach will provide a solution for other short-term or long-term stressors remains to be determined. Although this particular method is unlikely to be acceptable to the public, it may represent a useful principle awaiting alternative delivery.

Consequences of nutritional imbalances

Despite the many research programmes dedicated to identifying biochemical indicators of 'ideal' nutrition, the most reliable parameter remains change in body condition score and in many situations this correlates very well with fertility parameters (Beam and Butler, 1999). Reliance on fodder especially in beef animals and in dairy herds running milk-from-grass systems necessitates close assessment of soil mineral profiles in some regions, often only detected during investigations of subfertility. However, little is known about exactly how such deficiencies or excesses lead to aberrations in a multitude of varied reproductive processes (Smith and Akinbamijo, 2000). Although there is undoubtedly a need to understand the mechanism by which these mineral aberrations lower fertility, the major dietary components of energy and protein have greatest impact. Genetic selection has imposed considerable demands for increased nutritional support of much greater milk and meat production. Provision of protected fats has been offered as one solution with an impact on reproduction, particularly follicular growth (Beam and Butler, 1999).

At the cellular level, the provision of glucose involves both entry into the cell via glucose transporters (Williams *et al.*, 2001) and appropriate utilization involving both insulin and insulin-like growth factors (IGFs). Indeed, considerable effort has recently identified a role for IGFs and binding proteins in follicle selection, but is this cause or effect? In addition to the IGF system, a range of follicular growth factors has been implicated in the regulation of follicular growth, including the transforming growth factor β (TGF-β) superfamily, cytokines and bone morphogenetic proteins (Webb *et al.*, 1999; Souza *et al.*, 2002). At the molecular level, the development of multi-array systems and comprehensive bovine cDNA libraries should lead to the identification of all genes that are regulated during ovarian follicle emergence and selection.

Impact of clinical conditions

The creation of larger cattle units (dairy or beef) and increased animal and gamete movements world-wide render herds more susceptible to infectious diseases. From a specific reproductive prospective, *Trypanosoma congolense* has been localized in pituitary tissues and thus disrupts normal function (Abebe *et al.*, 1993); recent exposure to *Leptospira hardjo* reduces fertility (Dhaliwal *et al.*, 1996), bovine viral diarrhoea virus (BVDv) reduces progesterone secretion from the corpus luteum (Fray *et al.*, 2002) and *Neospora canium* has been associated with increased incidence of abortion (Williams *et al.*, 2000). The economic impact of these diseases must not be underestimated. Although vaccination and changes in farm management are proving useful, a greater understanding of the epidemiology of these diseases and prevention of transmission during artificial reproductive procedures is imperative. An indication of the prevalence of important diseases in the UK is given (Fig. 1).

Painful conditions, such as lameness or mastitis, are associated with reduced fertility (Dobson and Smith, 1998; Huszenicza *et al.*, 1998). Acute and chronic activation of the hypothalamus–pituitary–adrenal gland interferes with the regulatory mechanisms of reproduction. Precisely how this interference is mediated is still unknown but it undoubtedly concerns neuroendocrine mechanisms (Smith *et al.*, 2003) and possibly distorted immune regulation. Even before clinical abnormalities are evident, subclinical diseases affect fertility. A remarkable feature of cattle is the almost ubiquitous bacterial contamination of the uterine lumen within the first 2 weeks after parturition. Greater uterine bacterial contamination is associated with reduced ovarian follicular growth and function (Sheldon *et al.*, 2002).

There are other situations in which the uterus influences ovarian activity, for example immediately after parturition in most animals the first dominant follicle appears on the contralateral side to the previously pregnant uterine horn. However, it is interesting to note that cows have shorter calving-to-conception intervals if the first dominant follicle is selected on the ipsilateral ovary (99.0 ± 5.6 day versus 112.8 ± 4.4 days; Sheldon *et al.*, 2000). Exactly how the uterus (clean or infected) controls follicular growth requires further investigation. In contrast, the relationship between prevailing hormonal environment (progesterone or oestradiol) and uterine susceptibility to microbial contamination is still unclear (Subandrio *et al.*, 2000). The best way to reduce the impact of uterine infection requires urgent re-evaluation

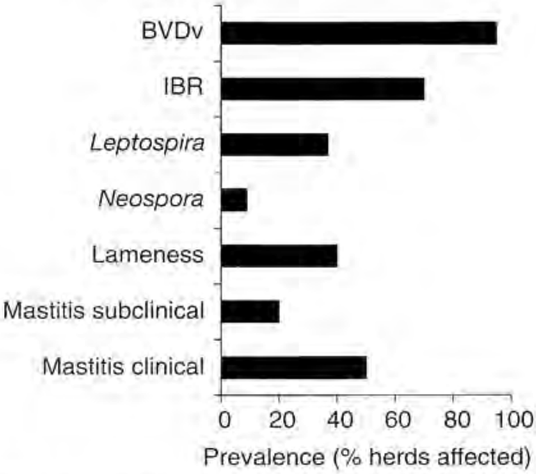

Fig. 1. Herd prevalence of infectious diseases and production diseases in the UK (data obtained from www.rdg.ac.uk/livestockdisea/cattle.htm). All of these diseases have an impact on the welfare of animals and on the financial viability of beef and dairy farming. BVDv: bovine viral diarrhoea virus; IBR: infectious bovine rhinotracheitis.

especially in view of the need to reduce the use of antibiotics (Dhaliwal *et al.*, 2001). Large-scale progesterone monitoring projects over the last 30 years indicate that the incidence of anovulation has not increased significantly with the decline in fertility (Royal *et al.*, 2000). However, there has been an increase from 14 to 35% in the number of prolonged luteal phases and it remains to be established whether this phenomenon is associated with an increased incidence of endometritis.

Overt infection of the uterus will disrupt the establishment of pregnancy both by the physical presence of large quantities of pus as well as altered immune responses that are so vital at the interface between the endometrium and the potentially antigenic trophoblast. This immunological interaction in the very early stages of pregnancy is clearly essential, but very little is known about the biochemical control mechanisms. The trophoblast produces an immune regulator, interferon tau, as part of the signal to indicate its presence to the dam and 'establish' pregnancy (Tysseling *et al.*, 1998; Leung *et al.*, 2001), but what are the precise immunological implications and how is pregnancy maintained after the demise of the influence of interferon at days 25–30 after fertilization? A fuller understanding of placental immunology is also important in the understanding of infectious abortion. Recent studies have shown that, to avoid maternal immune attack, fetal trophoblast cells down-regulate expression of the immunologically provocative molecules, MHC class I antigens (Bainbridge *et al.*, 2001). However, by suppressing MHC class I molecules, the trophoblast may be more susceptible to infection, as the physiological role of MHC class I is to present fragments of intracellular pathogens to the immune system to induce an acquired immune response. This phenomenon may explain why placental trophoblast cells of many species are especially susceptible to infection by a heterogeneous group of intracellular pathogens. Most of these organisms (for example *Neospora* and *Toxoplasma* in ruminants) can infect many body tissues, but it is infections of the pregnant uterus that are most devastating.

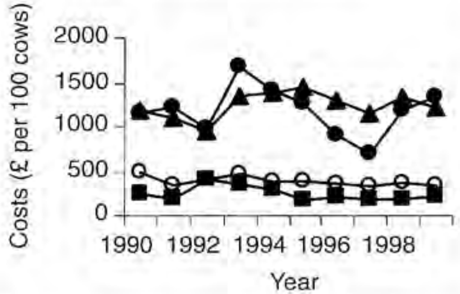

Fig. 2. Annual costs (£ per 100 cows) of common production diseases (●) subfertility; (▲) mastitis; (○) lameness; and (■) hypocalcaemia over 9 years in 52 sentinel commercial dairy herds in the UK (R. J. Esslemont, personal communication).

Difficulties at calving (dystocia, hypocalcaemia, ketosis) predispose cows to subsequent subfertility (Dobson and Smith, 2001) and there are economic costs for common production diseases (Fig. 2). Evidence is emerging to show that dominant follicles at days 35–50 after the clinical events at calving are smaller than those in normal herd-mates (W. Clark, R. F. Smith and H. Dobson, unpublished). Resumption of ovarian cyclicity after parturition has long-term consequences for subsequent fertility. A dominant follicle is usually selected in cows within 14 days after parturition but what subsequently happens to that follicle is crucial (Sheldon *et al.*, 2002). In a few beef cattle, but in most dairy cattle (46–70%), the first follicle undergoes a 5–8 day dominant phase, ovulates and establishes a typical post-parturition corpus luteum that has a duration of 9–12 days. This phase is followed by waves of new normal follicles and re-establishment of uneventful ovarian cyclicity. In the remaining animals, the first dominant follicle fails to ovulate; many follicles become atretic and repeated follicular waves ensue until conditions are more appropriate for ovulation, that is, usually the restoration of energy balance (Beam and Butler, 1999). This negative energy balance is a likely explanation for the greater proportion of beef cattle in which dominant follicles fail to ovulate after parturition (Murphy *et al.*, 1990). However, in up to 23% of dairy cows, the dominant follicle fails to ovulate but continues to persist with the formation of a 'cyst'. Ovulatory failure probably occurs because of the inhibition of an appropriate LH surge, although further studies are required to determine how and why this occurs (Ward *et al.*, 2000). Although the prevalence of cystic ovaries is not very high, the effects on fertility are devastating – calving to conception intervals are increased to >140 days (Borsberry and Dobson, 1989).

Reflection on all the above short- and long-term risks encountered at calving questions the necessity of such frequent repetition of the event. Within the dairy industry, a greater understanding of extended lactations and exogenous pharmacological induction of lactation is required – both from a mammary gland perspective and with respect to subsequent fertility (Arbel *et al.*, 2001). For example, what is the correct procedure for the exogenous hormonal induction of lactation; how long can the bovine alveolar epithelium maintain efficient output; are cows less fertile after insemination at >150 days after parturition? In the beef industry, the number of calves sold per grass-growing season is critical. Therefore, if pregnancy diagnosis could predict accurately the number of fetuses after precise induction of twinning (itself still a scientific challenge), nutrition could be adjusted appropriately and two offspring could be sold every 2 years with exposure of the dam to one fewer 'risky' calving.

Importance of oestrous detection

Artificial insemination, initially introduced to overcome the deleterious impact of venereal diseases, has effectively reduced the number of bulls on cattle establishments. Close monitoring of behavioural changes is now essential but low rates of submission for insemination are often due to human error especially with the reduction in numbers of personnel on farms (Nebel *et al.*, 2000). However, the intensity of oestrous expression varies both between and within animals at different times. It is possible that the intensity of expression is reduced as a consequence of lowered oestradiol exposure that is in turn due to decreased LH pulsatility during periods of inadequate nutrition or of stress (Fig. 3; Beam and Butler, 1999; Dobson *et al.*, 2000). In view of the importance to the modern cattle industry, it is regrettable that so little is known about the expression of behaviour in this species, especially the unusual homosexual mounting activity.

Pheromones are produced from the vagina by the oestrous cow, but the exact identities and control of synthesis are unknown (Rekwot *et al.*, 2001). Similarly, the physiology of pheromone detection in either bulls or other females has not been investigated. The vomeronasal organ in the roof of the mouth is involved, but how is the efficiency of this system controlled (Meredith, 1998)? Oestradiol is the classic hormone associated with behavioural oestrus, but which centres of the brain monitor changes in concentration and translate the hormonal message into behavioural changes? In ewes, the medial basal hypothalamus clearly plays a role and the continued secretion of GnRH for 24 h after the LH surge at oestrus may have behavioural implications (Caraty *et al.*, 2002). However, hypotheses to elucidate the hormonal control of oestrous behaviour will have to accommodate the phenomenon of oestrus in pregnancy. Approximately 8–10% of pregnant cows express oestrus and allow mounting by a bull, and yet peripheral progesterone concentrations remain high and vaginal mucus does not have typical oestrous 'ferning' properties (Thomas and Dobson, 1989).

Chemical communication between individuals has other implications for reproductive efficiency – fear, especially psychological, in a stressful situation can be expressed to other animals pheromonally and by aversive behaviour. This finding has implications for the stability of the herd hierarchical structure which influences fertility in dairy cows (Dobson and Smith, 1998).

Attempts to overcome poor oestrous detection in dairy cows include monitoring of progesterone in milk, either at critical times (selected days after parturition, day of insemination, or 20–24 days later) or serially to detect the decline in progesterone before impending oestrus (Dobson and Fitzpatrick, 1976; Lamming and Darwash, 1998). Technological advances have long promised the inclusion of 'chemical noses' to be placed in milking equipment but practical applications are still unavailable to the dairy industry (Pemberton *et al.*, 2001). Other potential aids include movement monitors (either pedometers or neck transponders) that record the extra physical activity associated with oestrus or telemetric pressure detectors placed on the backs of cows (Nebel *et al.*, 2000). With the advent of robotic milking machines and the attendant computerization, all these developments are acquiring more realistic expectations.

An alternative approach is to remove the need for oestrous detection by developing 'fixed time' or 'appointment breeding' insemination programmes that involve hormonal regimens to synchronize oestrus and insemination without regard to behaviour (Thatcher *et al.*, 2001). For use in the beef industry, presentations are so far impracticable and unimaginative, for example, a reduction in the number of required handlings and formulation as a 'pour-on' would facilitate application. Although the approach of 'blanket hormone treatment' is popular in the USA, there is considerable consumer resistance throughout Europe. The refinement of vaccinations to increase ovulation rates, such as immunization against ovarian feedback

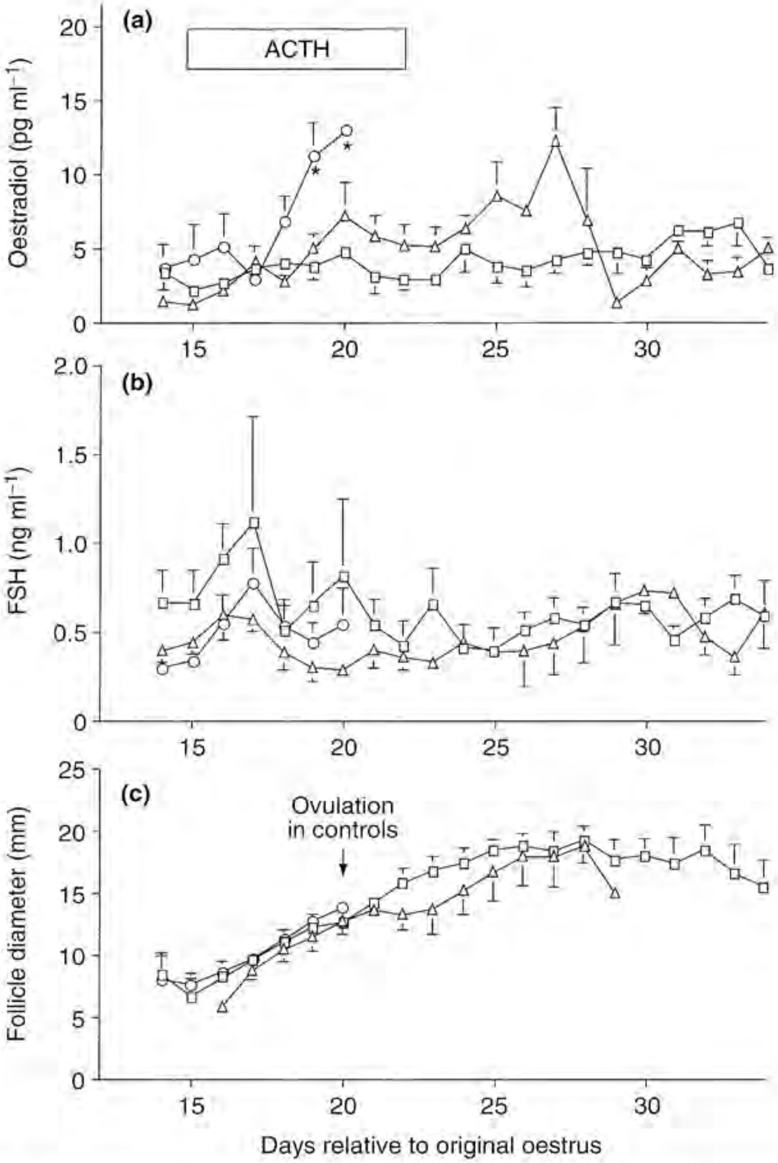

Fig. 3. Mean (± SEM) peripheral plasma concentrations of (a) oestradiol and (b) FSH, and (c) internal diameters of follicles in (○) six control heifers, (△) five heifers that formed an ovulatory persistent follicle and (□) six heifers that formed a prolonged persistent follicle after stress-simulation treatment with 100 iu ACTH at 12 h intervals for 7 days from day 15 of the oestrous cycle. Asterisks indicate that the control oestradiol concentrations were greater than those for prolonged or persistent follicles ($P < 0.05$). The low concentrations of oestradiol were associated with the absence of behavioural oestrus in all ACTH-treated animals. (Reproduced from Dobson *et al.* (2000) with permission.)

Table 1. Number and percentage of bovine uteri that contained a fetus at different stages of pregnancy on three different days in an abattoir

	Number of uteri	Percentage of all pregnant uteri
Total examined	2502	–
Number (%) with fetus	587 (24)	–
First trimester	141	24
Second trimester	288	49
Third trimester	158	27

Data from Singleton and Dobson (1995).

products as initially tested with sheep, or castration involving GnRH antisera or agonists, may provide alternative approaches (Hillard *et al.*, 1995; Bell *et al.*, 1997; D'Occhio *et al.*, 2000). Twinning would not be deleterious in cattle if farmers knew in advance (by accurate pregnancy diagnosis), so that appropriate diets can be provided in late pregnancy.

Significance of events during pregnancy and parturition

After the maternal recognition of pregnancy and the decline in interferon tau concentrations, further maintenance of pregnancy is accompanied by increased concentrations of pregnancy specific protein B (PSPB; also known as pregnancy associated glycoprotein, PAG). The role of these compounds is currently unknown even though their detection forms the basis of an efficient method of pregnancy diagnosis. However, the advent of detection techniques in milk, rather than the present requirement for blood, will improve user-friendliness (J. F. Bekers, personal communication). Nevertheless, monitoring PSPB profiles in blood has already increased understanding of the incidence and timing of early embryonic death (Szenci *et al.*, 1998).

Measurements of PSPB, progesterone or oestrone sulphate have been useful for the diagnosis of pregnancy, and accuracy is similar to that of manual palpation per rectum of the distended uterine horn. The application of transrectal ultrasonography has markedly improved the accuracy of pregnancy diagnosis, although the initial capital investment in equipment is high. There are additional benefits of being able to detect impending abortions and determine sex and age of the fetus (Boyd, 1995). However, despite all of these technological advances it is discouraging that 25% of cows sent to abattoirs are pregnant, even as late as the third trimester (Table 1; Singleton and Dobson, 1995). This finding is even more perplexing considering that approximately 30% of cattle are culled 'for failing to conceive'. The strategic use of accurate pregnancy diagnosis at all stages of pregnancy must be encouraged and reasons for the lack of use need to be analysed.

Problems at calving have to be identified quickly as early decisions to perform a Caesarean section and improved on-farm techniques lead to reduced losses (Cattell and Dobson, 1990). Just as judicious choice of bulls has improved milk yields for dairy cows, so genetic selection for fast early growth rates and improved carcass composition has increased perinatal losses (McQuirk *et al.*, 1998). The onset of parturition is under the control of the fetal pituitary–adrenal gland and recent studies in sheep have indicated that undernutrition at the time of insemination or in early pregnancy leads to delayed births, lower birth weights in twins, and other adverse health outcomes in later life (Hawkins *et al.*, 2000; Edwards and McMillen, 2002). Is this also the case for cattle? Furthermore, considering the importance of co-ordinated uterine contractions, cervical dilation and placental separation for an uncomplicated birth, it is remarkable that so little is known about the biochemical control of these mechanisms (Breeveld-Dwarkasing *et al.*, 2000).

The enigma of subfertility in bulls

There is considerable variation in fertility among bulls. In beef herds, the impact is often avoided by rotating teams of bulls. Regrettably there have been very few attempts to investigate the causes of bull infertility in contrast to the attention given to female subfertility. In the dairy industry, the main approach has been to select bulls for optimal freezability of semen; however, more still needs to be known about the deleterious effects of cryprotectants (Watson, 2000). As yet, there is no prominent characteristic that can be used to predict semen fertility although progress has been made with osmotic resistance tests, zona pellucida binding activities and IVF outcome (Revell and Mrode, 1994; Larsson and Rodriquez-Martinez, 2000). Interestingly, recent use of mixed semen straws from three different beef bulls has revealed the phenomenon of sperm competition – the understanding of which may shed light on new ways of improving bull fertility (S. Revell, personal communication). Furthermore, there is increasing evidence that there is a fertility-associated antigen on the sperm surface that is associated with an increase in pregnancy rates (66 versus 50%; Sprott *et al.*, 2000).

Considerable progress has been made over the past decade with methods for predetermining the sex of both semen and embryos (Seidel, 1999) – but practical application of both methods still requires efficient detection of oestrus. In addition, the conception rate after the use of 'sexed' frozen semen is low, but can be improved by deep uterine insemination, a difficult technique in itself. Nevertheless, refinement of sexing techniques to the point of matching the efficiency of natural insemination will revolutionize both cattle industries.

Reflection on attitudes of farmers

Many advances over the past 100 years have transformed cattle farming and the standard of required stockmanship. Artificial insemination has enabled significant genetic gains in both milk and meat quality and quantity. Nevertheless, this technique has introduced new problems, especially for oestrus detection as well as the consequences of genetic advances, such as greater reliance on unusual feedstuffs, to keep pace with the demands of increased output. The subsequent metabolic strain further challenges the cattle husbandry with an increase in body insults (for example, lameness, udder conformation) and a reduction in immune responses (for example, infectious diseases, mastitis).

How the farmer responds to these changes is very important. The nature of human character is vital when examining the relationship between man and animals (Seabrook and Wilkinson, 2000). In studies to examine the influence of farmers' character, the percentage of animals approaching within 3 m of a human observer is positively correlated with conception rate in dairy cows. Furthermore, fear displayed by stockmen elicits chronic stress in dairy cows, with consequences for (re)productive efficiency (Hemsworth *et al.*, 2000).

The viability of all livestock ventures depends heavily on human resources, and cattle farmers have responded positively to the many innovations that are evolving to maintain reproductive efficiency. However, on reflection, how much progress has been made during the 20th century? Aren't many of the recent 'improvements' merely overcoming the deficiencies imposed by domestication?

Conclusions

The reproductive challenges facing the cattle industries in this century are not intractable. Economic pressure to improve efficiency of both milk and meat production will dictate the rate of progress. This applies to both farms and research laboratories. Mistakes will be made, for example the large calf syndrome and the increasing incidence of metabolic and infectious diseases on farms. But some progress will also be made with a greater understanding of bovine reproductive biology and all the imposing interactions. It is salutary to read an article written in the middle of the last century to reflect on advances that have been made in the 20th century – and those that are still required in the 21st century (Hartman, 1960).

The authors are grateful to the many practising veterinary surgeons (especially the survivors of the Diploma course in Bovine Reproduction at the University of Liverpool) who have kept our research programmes clearly focused on the real problems encountered during bovine fertility work.

References

Abebe G, Shaw MK and Eley RM (1993) *Trypanosoma congolense* in the microvasculature of the pituitary gland of experimentally infected Boran cattle (*Bos indicus*) *Veterinary Pathology* **30** 401–409

Arbel R, Bigun Y, Ezra E, Sturman H and Hojman D (2001) The effect of extended calving intervals in high-yielding lactating cows on milk production and profitability *Journal of Dairy Science* **84** 600–608

Bainbridge DRJ, Sargent IL and Ellis SA (2001) Increased expression of major histocompatibility complex (MHC) class I transplantation antigens in bovine trophoblast cells before fusion with maternal cells *Reproduction* **122** 907–913

Beam SW and Butler WR (1999) Effects of energy balance on follicular development and first ovulation in postpartum dairy cows *Journal of Reproduction and Fertility Supplement* **54** 411–424

Bell M, Daley CA, Berry SL and Adams TE (1997) Pregnancy status and feedlot performance of beef heifers actively immunized against gonadotropin-releasing hormone *Journal of Animal Science* **75** 1185–1189

Borsberry S and Dobson H (1989) Periparturient diseases and their effects on reproductive performance in five dairy herds *Veterinary Record* **124** 217–219

Boyd JS (1995) Real-time diagnostic ultrasound in bovine reproduction. In *Veterinary Ultrasonography* pp 233–255 Ed. PJ Goddard. CAB International, Oxford, UK

Breeveld-Dwarkasing VNA, van der Weijden GC, Taverne MAM *et al*. (2000) The bovine cervix during the oestrous cycle: regional differences in morphology and density of steroid hormone receptors *Reproduction in Domestic Animals* **35** 120–124

Caraty A, Delaleu B, Chesneau D and Fabre-Nys C (2002) Sequential role of estradiol and GnRH for the expression of estrous behavior in ewes *Endocrinology* **143** 139–145

Cattell J and Dobson H (1990) A survey of caesarian operations on cattle carried out in general veterinary practice *Veterinary Record* **127** 395–399

Collick DW, Ward WR and Dobson H (1989) The association of types of lameness and fertility *Veterinary Record* **125** 103–106

D'Occhio MJ, Fordyce G, Whyte TR, Aspen WJ and Trigg TE (2000) Reproductive responses to GnRH agonists *Animal Reproduction Science* **60–61** 433–442

de Paz P, Sanchez AJ, De la Fuente J, Chamorro CA, Alvarez M, Anel E and Anel L (2001) Ultrastructural and cytochemical comparison between calf and cow oocytes *Theriogenology* **55** 1107–1116

Dhaliwal GS, Murray RD, Dobson H, Montgomery J and Ellis WA (1996) Reduced conception rates in dairy cattle associated with serological evidence of *Leptospira interrogans* serovar *hardjo* infection *Veterinary Record* **139** 110–114

Dhaliwal GS, Murray RD and Woldehiwet Z (2001) Some aspects of immunology of the bovine uterus related to treatments for endometritis *Animal Reproduction Science* **67** 135–152

Dobson H and Fitzpatrick RJ (1976) Clinical application of the progesterone-in-milk test *British Veterinary Journal* **132** 538–542

Dobson H and Smith RF (1998) Stress and subfertility *Reproduction in Domestic Animals* **33** 107–111

Dobson H and Smith RF (2001) What is stress, and how does it affect reproduction? *Animal Reproduction Science* **60–61** 743–752

Dobson H, Ribadu AY, Noble KM, Tebble JE and Ward WR (2000) Ultrasonography and hormone profiles of ACTH-induced persistent ovarian follicles (cysts) in cattle *Journal of Reproduction and Fertility* **120** 405–410

Edwards LJ and McMillen IC (2002) Impact of maternal undernutrition during the periconceptional period, fetal number, and fetal sex on the development of the hypothalamo-pituitary adrenal axis in sheep during late gestation *Biology of Reproduction* **66** 1562–1569

Fray MD, Mann GE, Bleach EC, Knight PG, Clarke MC and Charleston B (2002) Modulation of sex hormone secretion in cows by acute infection with bovine viral diarrhoea virus *Reproduction* **123** 281–289

Hartman CG (1960) Physiological mechanisms concerned with conception – an inventory of unanswered questions *Journal of Reproduction and Fertility* **1** 283–293

Hawkins P, Steyn C, McGarrigle HH, Calder NA, Saito T, Stratford LL, Noakes DE and Hanson MA (2000) Cardiovascular and hypothalamic–pituitary–adrenal axis development in late gestation fetal sheep and young lambs following modest maternal nutrient restriction in early gestation *Reproduction, Fertility and Development* **12** 443–456

Hemsworth PH, Coleman GJ, Barnett JL and Borg S (2000) Relationships between human–animal interactions and productivity of commercial dairy cows *Journal of Animal Science* **78** 2821–2831

Hillard MA, Wilkins JF, Cummins LJ, Bindon BM, Tsonis CG, Findlay JK and O'Shea T (1995) Immunological manipulation of ovulation rate for twinning in cattle *Journal of Reproduction and Fertility Supplement* **49** 351–364

Huszenicza G, Janosi S, Kulcsar M *et al*. (1998) Gram-negative mastitis in early lactation may interfere with ovarian and certain endocrine functions and metabolism in dairy cows *Reproduction in Domestic Animals* **33** 147–153

Jacobs MN and Lewis DF (2002) Steroid hormone receptors and dietary ligands: a selected review *Proceeding of the Nutrition Society* **61** 105–122

Larsson B and Rodriquez-Martinez H (2000) Can we use *in vitro* fertilization tests to predict sperm fertility? *Animal Reproduction Science* **60–61** 327–336

Leung ST, Cheng Z, Sheldrick EL, Derecka K, Flint AP and Wathes DC (2001) The effects of lipopolysaccharide and interleukins-1alpha, -2 and -6 on oxytocin receptor expression and prostaglandin production in bovine endometrium *Journal of Endocrinology* **168** 497–508

Lucy MC (2001) Reproductive loss in high-producing dairy cattle: where will it end? *Journal of Dairy Science* **84** 1277–1293

McQuirk BJ, Going I and Gilmour AR (1998) The genetic evaluation of beef sires used for crossing with dairy cows in the UK. II. Genetic parameters and sire merit predictions for calving survey traits *Animal Science* **66** 47–54

Meredith M (1998) Vomeronasal, olfactory, hormonal convergence in the brain. Cooperation or coincidence? *Annals of the New York Academy of Sciences* **855** 349–361

Murphy MG, Boland MP and Roche JF (1990) Pattern of follicular growth and resumption of ovarian activity in post-partum beef suckler cows *Journal of Reproduction and Fertility* **90** 523–533

Nebel RL, Dransfield MG, Jobst SM and Bame JH (2000) Automated electronic systems for the detection of oestrus and timing of AI in cattle *Animal Reproduction Science* **60–61** 713–723

Pemberton RM, Hart JP and Mottram TT (2001) An electrochemical immunosensor for milk progesterone using a continuous flow system *Biosensors and Bioelectronics* **16** 715–723

Pryce JE, Coffey MP and Simm G (2001) The relationship between body condition score and reproductive performance *Journal of Dairy Science* **84** 1508–1515

Rekwot PI, Ogwu D, Oyedipe EO and Sekoni VO (2001) The role of pheromones and biostimulation in animal reproduction *Animal Reproduction Science* **65** 157–170

Revell SG and Mrode RA (1994) An osmotic resistance test for bovine semen *Animal Reproduction Science* **36** 77–86

Royal MD, Darwash AO, Flint APE, Webb R, Woolliams JA and Lamming GE (2000) Declining fertility in dairy cattle: changes in traditional and endocrine parameters of fertility *Animal Science* **70** 487–501

Royal MD, Flint AP and Woolliams JA (2002) Genetic and phenotypic relationships among endocrine and traditional fertility traits and production traits in Holstein-Friesian dairy cows *Journal of Dairy Science* **85** 958–967

Seabrook MF and Wilkinson JM (2000) Stockpersons' attitudes to the husbandry of dairy cows *Veterinary Record* **147** 157–160

Seidel GE (1999) Sexing mammalian spermatozoa and embryos–state of the art *Journal of Reproduction and Fertility Supplement* **54** 477–487

Sheldon IM, Noakes DE and Dobson H (2000) The influence of ovarian activity and uterine involution determined by ultrasonography on subsequent reproductive performance *Theriogenology* **54** 409–419

Sheldon IM, Noakes DE, Rycroft AN, Pfeiffer DU and Dobson H (2002) Influence of uterine bacterial contamination after parturition on ovarian dominant follicle selection and follicle growth and function in cattle *Reproduction* **123** 837–845

Singh SS, Ward WR, Lautenbach K, Hughes JW and Murray RD (1993) Behaviour of first lactation and adult dairy cows while housed and at pasture and its relationship with sole lesions *Veterinary Record* **133** 469–474

Singleton GS and Dobson H (1995) A survey of the reasons for culling pregnant cows *Veterinary Record* **136** 162–165

Smith OB and Akinbamijo OO (2000) Micronutrients and reproduction in farm animals *Animal Reproduction Science* **60–61** 549–560

Smith RF, Ghuman SP, Evans N, Karsch FJ and Dobson H (2002) Stress and GnRH *Reproduction* **61** (in press)

Souza CJ, Campbell BK, McNeilly AS and Baird DT (2002) Effect of bone morphogenetic protein 2 (BMP2) on oestradiol and inhibin A production by sheep granulosa cells, and localization of BMP receptors in the ovary by immunohistochemistry *Reproduction* **123** 363–369

Sprott LR, Harris MD, Forrest DW, Young J, Zhang HM, Oyaro JN, Bellin ME and Ax RL (2000) Artificial insemination outcomes in beef females using bovine sperm with detectable fertility-associated antigen *Journal of Animal Science* **78** 795–798

Subandrio AL, Sheldon IM and Noakes DE (2000) Peripheral and intrauterine neutrophil function in the cow: the influence of endogenous and exogenous sex steroid hormones *Theriogenology* **53** 1591–1608

Szenci O, Beckers JF, Humblot P, Sulon J, Sasser G, Taverne MA, Varga J, Baltusen R and Schekk G (1998) Comparison of ultrasonography, bovine pregnancy-specific protein B, and bovine pregnancy-associated glycoprotein 1 tests for pregnancy detection in dairy cows *Theriogenology* **50** 77–88

Thatcher WW, Moreira F, Santos JE, Mattos RC, Lopes FL, Pancarci SM and Risco CA (2001) Effects of hormonal treatments on reproductive performance and embryo production *Theriogenology* **55** 75–89

Thomas I and Dobson H (1989) Oestrus during pregnancy in the cow *Veterinary Record* **124** 387–390

Tysseling KA, Thatcher WW, Bazer FW, Hansen PJ and Mirando MA (1998) Mechanisms regulating prostaglandin $F_{2\alpha}$ secretion from the bovine endometrium *Journal of Dairy Science* **81** 382–389

Vailes LD and Britt JH (1990) Influence of footing surface on mounting and other sexual behaviours of estrual Holstein cows *Journal of Animal Science* **68** 2333–2339

Ward WR, Ribadu AY, Harvey D and Dobson H (2000) Ultrasound and hormone profiles to monitor follicular activity in cattle after treatment with high doses of progesterone and oestradiol *Animal Science* **71** 577–583

Watson PF (2000) The causes of reduced fertility with cryopreserved semen *Animal Reproduction Science* **60–61** 481–492

Webb R, Campbell BK, Garverick HA, Gong JG, Gutierrez CG and Armstrong DG (1999) Molecular mechanisms regulating follicular recruitment and selection *Journal of Reproduction and Fertility Supplement* **54** 33–48

Williams DJ, Guy CS, McGarry JW, Guy F, Tasker L, Smith RF, MacEachern K, Cripps PJ, Kelly DF and Trees AJ (2000) *Neospora caninum*-associated abortion in cattle: the time of experimentally-induced parasitaemia during gestation determines foetal survival *Parasitology* **121** 347–358

Williams SA, Blache D, Martin GB, Foot R, Blackberry MA and Scaramuzzi RJ (2001) Effect of nutritional supplementation on quantities of glucose transporters 1 and 4 in sheep granulosa and theca cells *Reproduction* **122** 947–956

Wolfenson D, Roth Z and Meidan R (2000) Impaired reproduction in heat-stressed cattle: basic and applied aspects *Animal Reproduction Science* **60–61** 535–547