The AI Revolution of 1930s kickstarted livestock Inustry

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Contents

Phase I: The Early History (17th to 19th Century)

- The history of development of artificial insemination in cattle, etc, was reviewed (Allen 1985, Foote 2002, Moore and Hasler 2017).
- Sperms were first seen and called “animalcules” by an Italian (Leeuwenhoek (1678).
- First successful insemination was performed in a dog, which whelped three pups 62 d later (Spallanzani 1784).
- In several countries AI had been used in isolated studies with Rabbits, Dogs, and Horses and Seasonality of Reproduction (Heape 1897).
- This led to Cambridge becoming a world center for reproductive studies (Marshall, Hammond, Walton, and students such as M. C. Chang).
- Pioneering efforts were made to establish AI in Russia in 1899 (Ivanoff 1922).

Phase II: Technology Development (20th Century)

- Semen extenders were developed and technicians trained in Russia to select superior stallions and multiply their progeny through AI (Ivanov 1922).
- A special laboratory was established in Askania-Nova, where theoretical and practical courses of study were pursued on the physiology and biology of insemination and a body of specialists, mainly veterinary surgeons, was being trained for the practical application of this method on stud-farms and pairing stations.
- The work was taken over by Milovanov (1938,1964), establishing major projects for sheep and cattle breeding; designing and making artificial vaginas, etc. This replaced the earlier method of collecting semen from sponges placed in the vagina of mount animals.
- Milovanov motivated a Japanese scientist who returned and began AI program in horses in 1912 (Nishikawa, 1962). AI began to be applied in Japan in cattle, sheep, goats, swine, and poultry.
- Milovanov motivated Walton (1933) who produced ram semen in UK and shipped to Poland, which 2 d later was used for successful insemination of ewes.

Phase III: Kickstart through Coops (20th Century)

- Eduard Sørensen, at The Royal Vet College Denmark, familiar with the Russian work organized the first cooperative dairy AI organization in 1936 (Sorensen 1940).
- They enrolled 1,070 cows in the 1st yr and 59% conceived, slightly better than natural service in the same herds.
- They established the method of rectovaginal fixation of the cervix, allowing semen to be deposited deeply into the cervix or into the body of the uterus.
- This technique provided a tremendous advantage because fewer sperm were required for insemination of each cow.
- Another Danish “invention” was the straw for packaging semen, the cellophane straws. The French Straw is modified form of the Danish Straw (Cassou 1964).

Phase IV: Technology advancement

- An Italian resumed the efforts and developed an artificial vagina for dogs in 1914 (Perry, 1968).
- He, along with Lagerlof, launched the Int'l Cong AI and AR held every 4 yr.
- Lagerof completed his Ph.D. dissertation on changes in spermatozoa of bulls with impaired fertility (Lagerlof, 1934).
- He was motivated by WW Williams, a Cornell (US) DVM, who had published methods of staining spermatozoa.
- He established a group with worldwide influence in training veterinarians in the various aspects of fertility and AI.
- Other Scandanavians, such as Blom (1950), followed, publishing a steady stream of excellent papers on abnormal sperm morphology. These pioneers were all thinkers and doers, and they trained many who followed.

Phase V: Research integrated with commercialization

- Phenomenal growth of AI occurred in the 1940s in the United States (Foote 2002).
- In 1936, Brownell was inseminating cows in the Cornell herd (Sipher, 1991), and other AI work was started in the late 1930s in Minnesota and Wisconsin.
- In 1938, an AI cooperative was established in New Jersey, modeled after the Danish system (Perry, 1968).
- Another one in 1938 followed in the state of New York (Sipher, 1991).
- The development of the New York Artificial Breeders, Cooperative, Inc., currently Genex, Inc., in Ithaca, New York made possible the close collaboration between a farmer cooperative and researchers and extension personnel at Cornell University.
- This was a highly productive relationship resulting in the experimental insemination of hundreds of thousands of cows and publication of more than 100 research papers (Foote, 1998) on sire selection, testicular evaluation, semen collection, evaluation and processing; and fertility testing.

Phase VI: Technological Perfection - Semen Evaluation

- Assessment of the proportion of normal, progressively moving sperm is required for fertility assessment of bulls.
- A good microscope is the key.
- Later technologies developed, were:
  - Differential interference contrast microscopes
  - Multiple stains
  - Flow cytometry
  - Computer assisted sperm analysis (CASA)
- Post-thaw quality of frozen semen was evaluated (Saacke & Marshall, 1968).
- Semen volume is determined more accurately by weight; and stallion semen was weighed years ago (Nishikawa, 1959).
- Rapid optical density methods for measuring sperm concentration have replaced tedious hemocytometric procedures.
- Ejaculate volume and sperm concentration determine the number of sperm obtained.
- Fertility of sperm is determined through so many tests in addition to motility, morphology, hypoosmotic swelling test, mucous or gel penetration, and integrity of the DNA (Graham, 1978; Saacke, 1981).

Success Rates

- For commercial AI, an inexpensive method of estimating fertility, based on cows not returning for insemination, was developed (Thompson and Salisbury, 1947).
- This made possible the comparing of fertility of bulls, inseminators, semen processing procedures, and even herd performance.
- It provided a remarkable new system of recording breeding efficiency.
- Others had argued strongly for using pregnancy diagnosis, but it did not provide for centralized collection and evaluation of data.
- For commercial AI, an inexpensive method of estimating fertility, based on cows not returning for insemination, was developed as an essential component of the AI program (Thompson and Salisbury, 1947).
- This made possible the comparing of fertility of bulls, inseminators, semen processing procedures, and even herd performance under practical field conditions.
- It provided a remarkable new system of recording breeding efficiency.
- Pregnancy diagnosis was used as a tool but it did not provide for centralized collection and evaluation of data.

Semen Extension and Cooling

- US developed a yolk-phosphate semen extender (Phillips and Lardy, 1940).
- Salisbury et al. (1941) improved the media by buffering the egg yolk with sodium citrate.
- Sperm survival at 5°C permitted use of the semen for up to 3 d, and the citrate dispersed the fat globules in egg yolk, making sperm visible for microscopic examination.
- This semen extender was used worldwide for cattle.
- Glycerol was added later for cryopreservation of bull sperm.

Preventing Cold Shock and Disease Control

- Fertility was improved by 15% through protection of sperm from cold shock (Foote and Bratton, 1949) and the control of some venereal diseases by the addition of antibiotics (Almquist et al., 1949; Foote and Bratton, 1950).
- The Cornell University Extender (CUE, Foote and Bratton, 1950), containing the antibiotic mixture of penicillin, streptomycin, and poly- 4 Foote myxim B, was used for many years as the standard.
- This treatment of semen was worth hundreds of millions of dollars to the dairy world. No patents were filed, and neither Pennsylvania nor Cornell received any remuneration.
- Growth of AI was now ensured, because dairies using only AI eliminated venereal diseases, reduced embryonic death, and achieved high fertility.
- Sperm numbers per insemination with liquid semen were reduced from more than 100 m to 4 m (Salisbury et a, 1978; Foote, 1998).

The Role of Cornell University USA

- A century-long history was documented by Cornell University (CU, Foote 2023).
- **Samuel Leonard (26 November 1905 - 11 November 2007)**
  - Played a key role in developing the birth control pill -- which liberated women's sexual attitudes.
  - Used estrogen as a contraceptive, prevented pregnancy in rats with the female sex hormone.
- **Sydney Arthur Asdell (23 August 1897 - 21 February 1987)**
  - Established the basis for AI, IVF&ET, rates of gametes transportation through reproductive tract.
  - Initiated measurement of blood levels of the major reproductive hormones in cattle.
- **Glenn Wade Salisbury (2 June 1910 - 3 February 1994)**
  - Developed sound principles and procedures for AI that become the most powerful biotechnology used worldwide for the improvement of cattle with semen from genetically superior sires.
  - The guiding principles exemplified by Salisbury were good basic research, integrity, and superior accomplishment.
- **Robert Hutchinson Foote (22 August 1922 - 27 October 2008)**
  - Gamete and embryo biology, development of semen extenders, commercial use of AI in dairy cattle.
  - Treated bull semen with a combination of antibiotics-and ultimately helped to wipe out Vibrio fetus

Genetic Selection of Bulls for Milk

- AI utilized the genetically elite males for enhancing average herd milk production.
- Democracy in action? The elite bulls would not be limited to the wealthy.
- Robertson and Rendel (1950) in Scotland and Henderson (1954) at Cornell University pioneered new methods of sire selection.
- Henderson continued his research to establish the principles required for optimal sire selection programs and to provide objective methods for adjusting records for unequal environmental influences.
- He combined his efforts with his mathematical genius and attracted graduate students and scholars from all over the world.
- Along with these scholars, Henderson has had the greatest impact on dairy cattle genetics of any single person in history.
- He was a modest individual, always ready to take time with a yellow pad of paper to scratch out a solution to anyone’s mathematical problem. He didn’t need modern computers because he was born with one.

Semen Freezing and Packaging

- In England (Polge et al., 1949) reported the successful freezing of chicken sperm using the original yolk-citrate extender (Salisbury et al., 1941) plus glycerol.
- Almquist and coworkers (O'Dell and Almquist, 1957) developed whole milk-glycerol as a good medium to cryopreserve bull sperm.
- Tris-buffered egg yolk-glycerol also provided excellent protection for sperm either frozen or unfrozen (Foote, 1998).
- This soon became the most commonly used medium worldwide for cryopreservation of bull sperm and sperm from several other species (Iritani, 1980).
- Cassou (1964) developed a method for sealing plastic straws and a gun for insemination (Pickett and Berndtson, 1974).
- Originally 0.5-mL capacity straws were used, but 0.25-mL straws are popular because they require less storage space.

Estrus Detection, Synchronization, and Timing of AI

- The classic rule referred to as the AM to PM and PM to AM system for insemination was established by Trimberger (1948).
- Intensive research to regulate the time of estrus and ovulation in the cow has been ongoing for about 50 yr (Ulberg et al., 1951).
- Fertility was very low in early studies on estrus synchronization (Hansel and Convey, 1983).
- Cows can be inseminated at a fixed time without detection of estrus (Nebel et al., 2000).
- Rowson (1971) predicted that AI, combined with superovulation, synchronization of estrus, and manipulation of embryos would lead to major advances in animal production beyond the use of AI alone.
- Hodgson (1963) reported number of cows decreased by about 43%, but number of herds decreased by about 85% over the past 20 yr in the United States. Hence, number of cows per cowman has increased.
- Failure to detect cows in estrus by 60 to 90 days postpa~am has been related to observation failure rather than to failure of the cow to express estrus (Lauderdale JW, 1974).
- Prostaglandins could be used effectively as aids to detection of estrus, possibly even negating necessity for estrus detection. Initiation of breeding between 40 and 60 days postpartum would be another effective means of attaining calving intervals of 12 mo.

AI in Beef Cattle

- Beef cows are not managed as conveniently for AI as dairy cows. Many cows are on extensive ranges where detection of estrus and rounding up animals in estrus for insemination is not cost-effective and the proportion of beef cattle bred by AI is low (Foote, 2002, 1981).
- Where small groups of beef cows are kept in close confinement, estrous synchronize and fixed time insemination may be useful; in crossbreeding programs, AI has the advantage because semen can inexpensively replace maintaining bulls of separate breeds.
- Oklahoma State University developed these guidelines for Artificial Insemination for Beef Cattle ():
  - **Insemination technique:** developing through live animal practice, the ability to skillfully and accurately place semen at the proper location within the reproductive tract using sanitary and correct techniques.
  - **Semen handling:** developing through practice, the ability to properly handle, thaw and prepare semen for insemination, according to the recommendations of semen-producing organizations.
  - **Reproductive management:** training in the importance of heat detection, herd health, and total herd management for the development and continued success of an AI program.

AI in Sheep and Goats

- The early development of AI in sheep on a major scale began in Russia (Milovanov, 1938), where the collective farms provided an ideal arrangement for establishing AI programs.
- China also has extensive sheep AI programs.
- Artificial insemination spread to central Europe and also was widely applied commercially in France and Brazil (Foote, 1999).
- The techniques for semen collection and artificial insemination in sheep and goats have been described in detail (Evans and Maxwell, 1987).
- Semen quality and breeding efficiency are affected by season.
- Obtaining semen from a large number of rams in the field, electroejaculation is a useful procedure, applied to many species (Dziuk et al., 1954).
- Much of the early research in the Western world on extenders for sperm, freezing of semen, and AI techniques was done in Australia and France (Corteel, 1981).
- The techniques and media for freezing ram and buck semen such as with egg yolk-tris-glycerol were modified (Corteel, 1981) from procedures developed for bull sperm.

AI in Buffaloes

- Recent developments in buffalo reproduction and artificial insemination were reviewed (Warriach et al, 2015).
- Buffalo attain puberty when they reach about 60% of their adult body weight, but the age at puberty (AAP) can be ranging from 18 to 46 months (Jainudeen and Hafez, 1993).
- Genotype, nutrition & climate affect AAP & could be attained at 21-24 months in swamp buffalo (Borghese, 2005).
- The duration of the oestrous cycle exhibit a mean of around 21 days (Jainudeen and Hafez, 1993).
- Ovarian follicular dynamics during the oestrous cycle is similar to cattle. Studies from India, Brazil and Pakistan have shown that the majority of buffalo have two waves of follicular activity during their oestrous cycle (Warriach et al, 2015).
- The mean age of sexually maturity was 24.9±0.9 months in the Nili-Ravi buffalo bulls and the sexually quiescent period (prepubertal) extended up to 15 months and the presence of motile sperm in the ejaculate is attained at about 25 months (Ahmad 1984).
- Pregnancy rates (50%) were achieved with sexed semen containing 4 million spermatozoa (Gaviraghi et al., 2013).
- Excess intake of crude protein, associated with higher serum urea levels and low energy intake, associated with poor body condition, are the key factors for low reproductive efficiency and may be corrected by adopting a proper feeding strategy (Qureshi et al 2002).
- Qureshi et al (2007) reported that pregnancy depresses milk yield in dairy buffaloes.
- A lower reproductive efficiency under the peri-urban farming system was reflected by silent estrus in 51.5% of buffaloes. Increasing suckling duration and use of oxytocin delayed postpartum ovulation interval (Qureshi 2008).

Phase VII. The Advent of Biotechnology - Sexed Semen

- X-chromosome and Y-chromosome bearing spermatozoa develop to male and female embryo, respectively, after fertilization of the ovum. “The most sought after reproductive biotechnology of all time, selection of sex at conception, has a long history of great optimism, along with many disappointments” (Garner and Seide (2008).
- Many unsuccessful studies and a large number of inoperative registered patents for the sex separation of sperm cells, based on a variety of different principles, have been produced in past 50 yr.
- Currently, only the separation of stained X- and Y-chromosome-bearing sperm by flow cytometry cell sorting has proven successful.
- The USDA laboratories in Beltsville, Maryland announced the live birth of rabbits, with 94% female pups, from sexed sperm (Johnson et al. (1989)).
- It led to a US patent covering the technical details of flow sorting sperm for sex (Johnson, 1992).
- More than 200 patents related to all aspects of the production, freezing, and use of sexed bovine sperm have been registered by XY LLC) and Sexing Technologies (Navasota, TX).

Saving endangered species

- Reproductive biotechnologies was reviewed for conservation of endangered mammalian species (Andrabi and Maxwell, 2007).
- IUCN Red List notified 1528 animal species as critically threatened, including 162 species of mammals; 70 species of mammmalia were completely wiped out within last few years.
- In situ and ex situ conservation programs can benefit from assisted reproductive techniques (ART) including artificial insemination (AI), embryo transfer (ET), in vitro fertilization (IVF), gamete/embryo micromanipulation, semen/embryo sexing, genome resource banking (GRB), cloning or somatic cell nuclear transfer (SCNT)
- ET was first used by Kraemer et al. (1976) to produce a baboon infant
- Application of reproductive biotechnologies for endangered free-living animals is rarer than domestic breeds.
- Progress in ART for non-domestic species will continue at a slow pace due to limited resources, but also because the management and conservation of endangered species is biologically quite complex.
- In practice, current reproductive biotechnologies are species-specific or inefficient for many endangered animals, and this is because of insufficient knowledge on basic reproductive physiology.

Stress Physiology at Dairy Science Park

- Seasonality of Reproduction in thoroughbred mares was reported (Heape 1897).
- Onset of breeding season in dairy buffaloes was associated with increasing metabolizable energy (MEI) and decreasing crude protein (CPI) and minerals intake (Qureshi et al, 1999).
- Dairy animals in the tropics face numerous challenges under stressful tropical environments. So the animal has to re-visit its priorities for the body. Reproduction gets the last priority for nutritional partitioning and hence it is the first to be affected by stress (Qureshi, 2012).
- Hypothalamus-Pituitary-Gonadal (APG) Axis and Hypothalamus-Pituitary-Adrenal (HPA) Axis work alternatively; requiring freedom of the animals from stress to maintain normal reproductive activities.
- Feed supplementation prevented post-conception decline in milk progesterone concentrations associated with production stress in dairy buffaloes (Bubalus bubalis, Khan et al, 2009).
- Cows calving in summer showed lowest calving interval (Ihsanullah et al, 2020). Crossbred cows with 50% exotic blood showed earliest age at first calving and a constant upward trend in peak daily milk yield from first through sixth parity with a change of 18%. The finding may help the farmers in culling of unwanted animals.
- Zinc sulphate at the rate of 100 mg/buck/day improved semen traits and seminal plasma antioxidant capacity in Beetal bucks (Rahman 2014).

Stress Physiology at Dairy Science Park (contd)

- Holstein Frisian and crossbred cows showed more favorable response to vitamin E supplementation in respect of expression of stress and reproductive markers suggesting regular feeding of antioxidant to these breeds for better performance (Khan et al, 2016).
- Heat stress increased blood cortisol and protein, and reduced milk yield in dairy cows irrespective of the genetic makeup. In addition, there was no significant difference in blood metabolites and daily milk yield in the different levels of genetic makeup cows (Ihsanullah et al, 2017).
- Vitamin E and Se supplementation improved the physiological, hormonal and antioxidant status in Damani and Balkhi sheep. In addition, Damani sheep were more tolerant to heat stress than Balkhi sheep (Khan et al, 2017).
- Supplementation of diets with betaine improved broiler feed intake, weight gain, FCR and increased immunity were under heat stress condition (Chand et al, 2017).
- Better BCS and increased lactation stage had significant impact on milk yield, stress reduction and restoration of ovarian activity in buffaloes during postpartum period (Saqib el al, 2022).
- Caprine GDF9 gene could be used as a candidate gene for litter size, milk production and body measurement traits in Damani goats through marker-assisted selection for future breeding program (Ullah et al, 2022).

Boosting livestock production through MOET

- Reproductive biotechnology options for improving livestock production, were reviewed (Hadgu & Fesseha, 2020).
- Various ARTs have been developed to obtain a large number of offspring from genetically superior animals.
- *Multiple ovulation and embryo transfer (MOET)* aims to fertilize several oocytes in to produce more viable embryos, which are transferred into the recipient, resulting in a higher birth rate.
- The first three generations of reproductive biotechnologies have been: i) Estrous synchronization and; ii) AI in beef producers for over 50-years; and iii) Embryo transfer since 1975 (Thibier 2005).
- *Estrus synchronization* is an alternative strategy to bypass the critical problem of estrus detection and it is the process of bringing female animals to the heat state of those having preovulatory follicular activity using hormonal interventions and helps for timely insemination to increase conception rate (Paul et al, 2015).
- *Embryo transfer* (ET) is a process by which an embryo is collected from a donor female and then transferred into a recipient female where it completes its development.
- It is the most commonly used biotechnology after AI and ES and is profitable for producers of pure-bred animals and genetically superior females and AI bulls.
- Embryo transfer is very expensive and many of the basic procedures were established some years ago. Little academic research currently is being conducted that is likely to immediately benefit the commercial industry.
- Because success rates in well-managed cattle herds are generally quite high, most recent improvements involve rather small, albeit important, increments (Betteridg 2003).

MOET (contd)

- *Selecting donors cows:* Genetically superior animals that contribute to the objectives of the program and production of more embryos, are the two broad criteria for selecting donor cows for most embryo transfer programs (Thibier 2006).
- Selecting the male is usually more important than selecting the donor female.
- The donor female is injected with FSH, twice daily for four days in the range of eight to fourteen days. A PGF2α injection is given on the d4 of the schedule for CL regression and estrus occurrence 48-hours later.
- Multiple follicles should be developed on the ovaries.
- The donor may be inseminated; embryos collected non-surgically six to eight-days after breeding; evaluated and transferred to the recipient.
- *Recipient cows* are reproductively sound, exhibit calving ease, and have good milking and mothering ability.
- Proper recipient herd management is critical to ET success and requires understanding of the nutrition and estrus synchronization.
- To maximize embryo survival in the recipient, conditions in her reproductive tract should resemble donor.
- Recipients synchronized with PGF2α must be treated 12 to 24-hours before donor cows as the induced estrus will occur in recipients in 60 to 72-hours and in superovulated donors in 36 to 48-hours.

In vitro Fertilization (IVF)

- The fertilization of the sperm and the egg is conducted in vitro at specific environmental and biochemical conditions (Cowan and Becker 2010).
- Unfertilized eggs (oocytes) is removed from the donor cow's ovaries, usually recovering 6-8 useable oocytes.
- The oocytes mature in an incubator and are fertilized with sperm.
- The resulting zygotes incubate and develop in the laboratory before being placed into the recipient cow.
- In vitro fertilization of the oocytes is usually carried out following 24-hour maturation in the IVM medium.
- Surrounding cumulus cells are removed by gentle pipetting and washing in fertilization medium and groups of 40-50 oocytes are placed in 4-well dishes in 500 µl of synthetic oviductal fluid covered by 200 µl of mineral oil.
- Motile sperm are obtained by centrifugation of frozen thawed semen in the percoll gradient (45%/90%) at 500 grams for 10-minutes at room temperature.
- Percoll gradient separation of spermatozoa seems to be an effective means of yielding motile sperm from frozen-thawed semen.
- Although 17-hour coincubation is practiced in IVF, it has been shown that even 4-hour coincubation was enough to obtain acceptable cleavage and blastocyst rates in sheep (O'Brien J et al, 2003)

Sexed Embryos

- Sexual differentiation of the embryo is determined by the presence or absence of elements normally located on the Y-chromosome (Hadgu and Fesseha, 2020).
- Some of the techniques employed commercially for the embryo sexing are:
  - Chromosomal analysis of demi-embryos
  - Immunological detection of embryonic H- Y antigen
  - Use of Y-specific probes
  - Fluorescence in situ hybridization
  - Sexing of preimplantation embryos using loop-mediated isothermal amplification (LAMP)
  - Ultrasonic examination of fetal structures.
- Predetermination of the sex of offspring provides a greater number of males or females and helps in the selection of individuals with top genetic makeup for improvement in next generation
- Known sex of embryos produced for use in ET programs can more effectively help to manage producer resources because more heifer calves per ET can be produced.

Ovum Pick Up

- Ovum Pick Up (OPU) is a non-invasive and repeatable technique used for recovering large numbers of competent oocytes from antral follicles of live animals (Choudhry et al 2016).
- This procedure was first done in cattle by Galli *et al (*2001), which was later tried in other species as well.
- Embryo production from ovum pick-up oocytes is affected by age, season, FSH stimulation and can average 1-3 embryos developed from oocytes collected per session.
- OPU can be performed without side effects both in cattle and buffaloes with a minimal stress to the animal.
- In India, the first buffalo calf (Saubhagya) was produced through this technique by Prasad et al (2013), and subsequently, first bovine calf (Holi) was produced at ICAR-National Dairy Research Institute.
- OPU has advantage to collect oocytes from animals with less invasiveness and the use of superior animals as oocyte donors in embryo transfer (Purohit et al, 2003).
- This method not only increases the lifetime reproductive efficiency but also can be used in follicle ablation for aiding follicle turnover during embryo transfer protocol.
- Follicular aspiration also allows studying the molecular intricacy and the role of various cytokines during folliculogenesis.

Cloning

- Producing genetically identical individuals to donor cells and copying gene, that involves the creation of an animal or individual that derives its genes from a single other individual; also referred as “Asexual reproduction” (Reik 2007) or: the deliberate production of genetically identical individuals (NIH-NLM).
- Embryo splitting and nuclear transfer are methods of cloning, where an embryo is split at the 6-to 8-cell stage, where it can be used as an expansion of IVF to increase the number of available embryos.
- Helps preserve indigenous breed of livestock, that have production trial and adaptability to local environments that should not be lost from the global gene pool.
- It also enables the rapid dissemination of superior genotypes from nucleus breeding flock and herds, directly to commercial farmers.
- Somatic cell nuclear transfer (SCNT) starts with the removal of the chromosomes from an egg to create an enucleated egg. The chromosomes are replaced with a nucleus taken from a somatic cell of the individual or embryo to be cloned (NIH-NLM).
- Infertile human couples may have a child that is genetically identical with one of them, or with another nucleus donor.
- Cloning of livestock is a means of replicating an existing favorable combination of traits, such as efficient growth and high milk production, without the genetic “lottery” and mixing that occur in sexual reproduction.

Transgenesis

- A transgenic animal is one that carries a foreign gene that has been deliberately inserted into its genome (Hadgu and Fesseha, 2020).
- Transgenic animals are genetically modified to contain a gene from a different species following gene transplantation or resulting from the molecular manipulations of endogenous genomic DNA.
- The new gene is inherited by offspring in the same way as the organism's own genes (Rajoriya R et al, 2013).
- There are different methods of transgenesis such as:
  - DNA microinjection
  - Sperm-mediated gene transfer
  - DNA Electroporation
- Transgenesis has been used in breeding and biomedicine like (Niemann et al 2005; Wells 2010):
  - Transgenic cows producing milk of increased âcaseine and ê-caseine content
  - Production of transgenic cows resistant to mastitis
  - Production of environment-friendly transgenic individuals as a model to understand various physiological processes in farm animals and humans

Marker-assisted selection

- Marker-assisted selection (MAS) is an indirect selection process of quantitative trait loci (QTLs) controlling a trait using a genetic marker in order to select a trait.
- There are three phases in the development of MAS programs:
  - *Detection Phase:* DNA polymorphisms are used as markers in order to detect specific allele frequencies. Markers associated with QTL are identified.
  - *Evaluation phase:* Linked markers are tested in target populations to determine whether QTL segregated within the population.
  - *Implementation phase:* Predictive linked markers in a population are used within families, and direct markers are used across families in order to produce a genotypic database.
- MAS is an aid in the detection of genes for disease resistance, product quality, genetic disorders, stress resistance, feather pecking, longevity, and desired behavioral characteristics.
- The Poll Gene Marker test developed in Australia has been adopted worldwide (CSIRO 2023). It is helping breeders to select for hornless cattle, which makes it safer for the animals themselves and the people handling them.

Embryogenomics

- This involves the study of genes' expression in various developmental stage embryos in natural and altered environmental conditions through novel biotech tools Choudhry et al (2016).
- Cascade of events during embryonic genome activation and development can be studied pertinent for early differentiation, successful implantation and fetal development.
- Various studies on the expression of marker genes, viz., glucose transporter Type 1, heat shock protein HSPA-1A, MATER, zygote arrest 1, growth differentiation factor 9, leukemia inhibitory factor, and bone morphogenetic protein, embryos/oocyte have been carried out.
- Analysis of the genes will aid in selecting markers for determining quality embryo and be useful to assess the embryo normalcy and optimize assisted reproductive technologies.
- Khan et al (2011) suggested that glucose is transported through GLUT1 from the maternal blood-stream for use as a placental fuel and for further transport through GLUT3 to the fetal circulation, thus signifying the distinct anatomical localization of GLUT1 and GLUT3 in the rabbit placenta during successful pregnancy.
- The expression of stem cell factor (SCF), an important regulator of Sertoli cell development, was increased by Anti Mullarian Hormones (AMH), which differentially regulates the fate of Sertoli cells in vitro by promoting proliferation at low concentrations and apoptosis at high concentrations (Rahman et al, 2017).

Stem Cells Technology - Setting the Aging Clock to Zero

- Stem cells are unspecialized cells of the human body; able to differentiate into any cell of an organism and have the ability of self-renewal; existing both in embryos and adult cells (Zakrzeski et al 2019).
- Totipotent stem cells are able to divide and differentiate into cells of the whole organism with highest differentiation potential; example is a zygote.
- These cells can later develop either into any of the three germ layers or form a placenta.
- After approximately 4 days, the blastocyst's inner cell mass becomes pluripotent stem cells (PSCs) and form cells of all germ layers but not extraembryonic structures, such as the placenta. Embryonic stem cells (ESCs) are an example.
- Currently, several stem cell therapies are possible, among which are treatments for spinal cord injury, heart failure, retinal and macular degeneration, tendon ruptures, and diabetes type 1.
- Multipotent haematopoietic stem cell transplantation is currently the most popular stem cell therapy, deriging target cells from the bone marrow, peripheral blood, or umbilical cord blood.
- There is a hypothesis that when human or mouse adult somatic cells are reprogrammed to induced pluripotent stem cells (iPSCs), their epigenetic age is virtually reset to zero. This was based on an epigenetic model, that at the time of fertilization, all marks of parenteral ageing are erased from the zygote's genome and its ageing clock is reset to zero.

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