SUMMARY

Spermatogenesis is a process of cell differentiation which transform the stem spermatogonia into final mature spermatozoa. It can be divided into three main phases :

1. spermatocytogenesis: By this mechanism, spermatogonia replenish their population and generate precursors of spermatogenesis by mitosis .
2. Meiosis : During this phase, the spermatocytes prepare for and undergo the complex maturation divisions aiming at :
    - Reducing chromosome number of germ cells by half forming male gamete that fertilize haploid ovum to regain the diploid chromosome pattern.
    - Generating genetic variations by exchanging segments of homologous chromosomes.

Spermiogenesis : It is the process of cytodifferentiation of spermatids into spermatozoa with no further cell division . During different cellular organeliles occur :

(a) formation of the acrosome.

(b) Development of the flagellum or tail.

(c) Nuclear changes.

(d) Reorganization of cell organelles and cytoplasm.

(e) release of spermatozoa from epithelium.

Spermatogenesis is a relatively inefficient process, typified by the death of up to half of the germ cells produced. This germ cell death occurs spontaneously during the whole phases of spermatogenesis.

Recent studies showed that the germ cell death during Spermatogenesis shows many apoptotic classic morphologic and biochemical features.

Apoptosis is a form of cell death based on a genetic mechanism characterized by a series of cellular, morphological and biochemical alterations that are completely different from those of necrosis (oncosis), the other principal pattern of cell

death. Apoptosis is responsible for cell death in several important physiologic as well as pathologic processes.

A cell undergoing apoptosis show characteristic morphologic changes as cell shrinkage, chromatin condensation, and formation of cytoplasmic blebs followed by phagocytosis of apoptotic bodies with no inflammation. It also show characterstic biochemical changes as protein hydrolysis by caspases, protein cross linking, DNA breakdown with characterstic ladder pattern appearance on electrophoresis.

1. **Extrinisic Cell Death Pathway** involving the interaction of a death receptor with it ligand.
2. **Intrinsic Cell Death Pathway** depending on the participation of mitochondria and is regulated by proapoptotic and antiapoptotic members of the Bcl-2 family.

The end result of either pathway is **caspase** activation and cleavage of specific cellular substrates, resulting in the

morphological and biochemical changes associated with the apoptotic phenotype.

Normal spermatogenesis represents a precisely regulated balance between continuous cell proliferation and concomitant programmed cell death, apoptosis .

Four possible functional roles have been proposed for the presence of apoptosis during normal spermatogenesis :

1. maintainance of an optimal germ cell/Sertoli's cell ratio.
2. Elimination of abnormal germ cells.
3. The formation of the blood-testis barrier.
4. Creation of a prepubertal apoptotic wave which facilitates the eventual functional development of mature spermatogenesis.

Apoptotic cell death seems to be strictly regulated by extrinsic and intrinsic factors (genetic regulators). Examples of extrinsic stimuli potentially important in testicular apoptosis are irradiation, chemotherapy, trauma, viral infection, toxin exposure, withdrawal of hormonal support, varicocele, heat and

aging . Whereas the intrinsic regulation of apoptotic process is under the control of several genes. They are either apoptosis inducing genes, as Fas, c-Myc, p53, Bax, or apoptosis suppressing genes, such as Bcl-2 and c-kit.

Recent studies demonstrated that the percentage of germ cells undergoing apoptosis in normal subjects is significantly lower than that seen in men with oligoashenoteratozoospermia, maturation arrest, hypospermatogenesis, varicocele, Hodgkin's disease, testicular seminoma, and infected AIDS patients.

It will be of interest to study the role of apoptosis and apoptosis regulatory proteins in male infertility as this may lead to new therapeutic modalities involving the reversal or inhibition of the apoptosis process.

Future Directions

Further characterization of specific, genetic testicular regulators responsible for altered apoptosis in human male

infertility may lead to gene therapy involving the reversal or inhibition of the apototic process. In this fashion, cells arrested at the spermatid stage may be matured into spermatozoa, potentially allowing the use of ICSI. Similarly, cells arrested at the secondary spermatocyte stage may be advanced to the round spermatid stage, allowing the use of technologies such as the presently experimental technique of round spermatid nuclear injection (ROSNI) .

Definition of the pathways that promote selective germ cell deletion may provide strategies for the protection and rescue of germ cells threatened by radiotherapy and chemotherapy. Protection of spermatogonial populations by hormonal manipulation before chemotherapy and radiotherapy has shown benefit in some animal models. This approach may be further enhanced and refined with a more complete understanding of the mediators of the apoptotic process in humans. The ability to induce a reversible increase in germ cell apoptosis might hold promise in the field of male contraception. Finally, identification

of the mechanisms by which the selective apoptotic elimination of chromosomally damaged or abnormal germ cells takes place may aid in the prevention of the transmission of genetic abnormalities to offspring.