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# Endocrine Aspect of Male Infertility

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Spermatogenesis may be suppressed by many factors such as x-ray irradiation, high temperature, metal poisoning, deficient food intake, some of metabolic and endocrine diseases and so on, resulting in decreased ability of fertility in male. Once the disturbance of spermatogenesis has occured in human beings, however, it is usually very difficult to determine the pathogenesis of infertility in many cases. Therefore, male infertility is usually defined as a condition of decreased fertility in male by unknown genesis.

In the present paper, the discussion will be focussed to the male infetility in the above sense.

**Anatomic structure and function of the testis**

Some features of anatomic structure of the testis should be recognized before discussing male infertility. The testis tissue consists of two major components; seminiferous tubules and interstitial tissue. The latter in mature testis tissue is abundant of Leydig cells which are major site of androgen biosynthesis in the testis and present close to tubular wall. The seminiferous tubules consist of tubular wall, Sertoli cells and germinal epithelium. The seminiferous tubule has at least two compartment system. The basal compartment contains the spermatogonia and pre-leptotene spermatocyte, and the inner compartment contains the other germ cells (Dym and Fawsett, 1970). These compartments are formed by Sertoli cells and their junctional complexes. Thus, the early designation of Sertoli cells as nurse cells is anatomically supported.

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**Regulation of spermatogensis**

Since excellent reviews have been described (Steinberger, 1971; Lipsett, 1976), a brief discussion will be presented here. In considering the hormonal control of spermatogenesis, it appears important to distinguish initiation, restoration and maintenance of spermatogenesis.

Probably, the best example of the initiation of spermatogenesis is hypogonadotropic hypogonadism. These patients show no evidence of either FSH or LH effects and their tubules remain completely primitive. In most of the cases reported, human chorionic gonadotrophin alone did not stimulated their spermatogenesis (Martin, 1967; MacLeod, 1970). The occasional effectiveness of human chorionic gonadotrophin may be attributed to the degree of FSH deficiency in these patients (Paulsen, 1668). So called "fertile enuchoidism" further suggests the requirment of hormones for initiation of spermatogenesis. The patient has almost normal level of FSH and low LH. On the other hand, the finding that spermatogenesis has stimulated at the site adjacent to Leydig cell tumor in prepubertal boys (Gittes et al., 1970; Steinberger et al., 1973) may suggest that testosterone may promote the initiation of sper-

matogenesis in concert with FSH, since low plasma FSH level is recognized in normal prepubertal boys.

Hormonal requirment for restoration of spermatogenesis is very similar to that of the initiation. Investigations have indicated the necessity of both FSH and LH or androgen for restoration of spermatogenesis in hypophysectomized animals (Go et al, 1971), and human beings (Mancini et al., 1971).

Once spermatogenesis has been initiated, testosterone appers to play an important role for the maintenance. Low doses of testosterone suppresses normal spermatogenesis of the rat, whereas either high doses or implantation of testosterone in the testis maintains it in the hypophysectomized rat (Boccabella, 1963; Berndtson et al., 1974, Ludwig, 1950). Testosterone concentrations in spermatic venous blood plasma is 40 to 50 times of peripheral blood. Accordingly, interstitlal fluid of the testis contains this level of testosterone. A replacement dose of testosterone to men decreases plasma LH and lowers Leydig cell function resulting in marked decrease of intertesticular testosterone level (Morse et al., 1973). Thus, these findings are harmonize together.

From the study of hypophysectomized men, androgen appears necessary for formation of primary spermatocytes from spermatogonia and FSH for maturation of spermatid (Mancini et al., 1971). Since FSH promote the formation of androgen binding protein in the Sertoli cell, androgen may possively promote spermiogenesis where androgen binding protein carries androgens.

### Site of hormone action at the seminiferous tubule

Many studies have been indicated direct effects of FSH and testosterone on the Sertoli cell in the absence or depletion of germ cells (Hansson et al., 1975). FSH increases adenylate cyclase activity in isolated seminiferous tubules even where the spermatogonia has been destroyed (Means, 1975; Dorrington and Fritz, 1974) and cAMP in the seminiferous tubule (Dorrington et al., 1972). Furthermore, FSH has been demonstrated to bind to Sertoli cells by immunhitologic technique (Castro et al., 1972) and to the tubule by isotope-labeled FSH preparation (Means, 1975), while LH does not bind to the isolated tubule.

As stated above, androgens profoundly concerns with function of seminiferous tubules. Actually, a specific androgen receptor has been demonstrated in cytoplasm and nucleus of rat seminiferous tubules (Mulder et al., 1975). The receptor has the characteristics similar to the receptor of prostate and seminal vesicles; namely high affinity, low capacity, translocation to the uncleus and inhibition by cyproterone. One important difference is the specificity to androgens. The receptor in tubules show approximately equal affinity for both testosterone and dihydrotestosterone, whereas the affinity of the prostate cytosol receptor for dihydrotestosterone is several times that for testosterone. The finding is in accordance with low 5$\alpha$-reductase activity in the mature testis when compared to that in the prostate. Therefore, it appears likely that testosterone is the active primate androgen at seminiferous tubules. On the other hand, there is a clinical evidence supporting the above. Patients with generalized 5$\alpha$-reductase deficiency, possively of hereditary defect, has been described (Imperato-McGinley et al., 1974). Although these patients manifest deformities of organs where 5$\alpha$-dihydrotesterone is necessary for embryonic development, spermatogenesis in their testis developes apparently normal at puberty.

Category of male infertility. ……What is oligospermia?

As stated in introduction, decrease or lack of fertiziling ability in male may manifest as a symptome of many kind of diseases, a result of poisoning and so on. Usually, efforts are made to the patient complaining infertility to find out the causative genesis, and then the patient without any findings of systemic diseases ais reffered for male infertility.

When sixty-one caucasian patients aged 21 to 44 years reffered for male infertility are examined, they were further divided into 5 subgroups; 1. clinically apparent varicocele, 2. defects of autosomal chromosome in lymphocytes, 3. azospermia with normal spermatogenesis which may be caused by obstruction of semina tract, 4. oligospermia with unknown genesis and 5. azospermia with aspermatogenesis (Nankin et al., 1977). Among these groups, 4th group of idiopathic oligospermia will be discussed further in the present paper.

Data described by Smith and Steinberger (1977) is of interest in relation to oligospermia. They compared sperm concentration in ejaculates obtained from husbands of infertile couples with those of fertile husbands requesting a vasectomy. Approximately 40% of fertile husbands had sperm count below 40 millions/ml, and 63% of husbands of infertile couples were oligospermia with sperm count below 40 millions /ml. Previous reports were consistent with the findings above (McLeod and Gold, 1951; Nelson and Bunge, 1974; Rehan et al., 1975). These results emphasize that both wives and hunsbands concern together profoundly with their fertility, and also arise a question whether so-called idiopathic oligospermia is a pathological or biological state. However, it is certain from these data that the higher the sperm count, there is the more possibility for conception. Therefore, it appears worth while to investigate oligospermics nonetheless whether it is a disease or not.

## Histologic findings of the testis of oligospermic men

Of 35 oligospermic men, the testis tissue biopsied from twelve were enough for both histologic and biochemical examination. Leydig cells, tubular wall and spermatogenesis were evaluated (Oshima et al., 1977).

The Leydig cell cluster present in relation to the number of tubules was determined. A cluster is defined as a contiguous, usually discrete group of Leydig cells. Where larger number of Leydig cells are present in a single area, the identification of each cluster is aided by the presence of a capillary in association with a small grouping of Leydig cells. The Leydig cell cluster index was obtained by counting all clusters in all fields of codded biopsies and dividing by the number of tubules present.

Spermatogenesis was evaluated using the germinal epithelium mean score count method of Johsen (1970).

The tubular wall of the seminiferous tubule was also evaluated by a score count. Each tubular wall was given a score from 5 to 1 as follows;

5=no hyalinization of tubular wall surrounding a tubule;

4=partly hyalinized tubular wall;

3=hyalinization totally surrounding the tubule with either undegenerated Sertoli or germ cells within;

2=hyalinization totally surrounding the tubule with only degenerated cells within;

1=completely hyalinized fibrosed tubule.

Initial examination of the biopsies suggested two groups of patients, 5 with abundant or

proliferative Leydig cells and 7 with sparse or few Leydig cells. By actual count, the Leydig cell cluster index ranged from 0.46 to 2.02 for the entire group. The patients were divided into two groups, one designated P for proliferative and the other n-P for non-proliferative. The P group had an average count of 1.3 cluster/tubule and the n-P group an average count of 0.6 cluster/tubule. There were no overlaps between the groups.

The mean germinal epithelium score and the mean tubular wall score count showed no significant differerence for the P and n-P groups.

### Endocrine porfile of oligcspermia

Serum concentration of FSH in oligcspermia have been recognized elevated with inverse correlation of sperm count in ejaculate (Hunter et al., 1974; Nankin et al., 1976) and show over-response to LRH administration (Isurugi, 1973). While mean value of plasm LH and testosterone in oligospermia are controversy (Hunter et al., 1974; Nankin et al, 1976). However, it should be noted that some cases of oligospermia have markedly high LH and low testosterone levels in their plasm.

The average sperm count for oligospermics in the present series was 7.3 millions/ml. There was no significant difference in the average value for the P and n-P groups. Also there were no significant differences in LH, FSH or testosterone levels between the P and n-P groups. When the oligospermic men were compared to the normal, control, FSH was significantly high both for the entire group and each subgroup. LH was higher than normal for the P group but not for the n-P group. Testosterone was lower than normal for the entire group but not for each group.

### Steroidogenesis

In the human testis, biosynthesis of testosterone from pregnenolone is carried out via $\Delta^5$ and $\Delta^4$-pathway. Immediately after biopsy, stroidgenesis studies were performed with $^{14}C$-labeled steroid substrate in the presence of excessive amount of required cofactors.

Formation of $\Delta^4$-3-oxosteroids from pregnenolone and 17$\alpha$-hydroxylated metabolites from either pregnenolone or progesterone were significantly greater in preparations from patients of the P-group than from the n-P group.

Although the formation of testosterone from androstenedione was greater in the P group than in the n-P group, the difference was not significant.

There were too few studies to permit comparison of C17-20 lyase activity between the P and n-P groups.

For the entire group of oligospermic men, there was a significant correlation between number of Leydig cell clusters and the amount of either $\Delta^4$-3-oxo-steroids or 17$\alpha$-hydroxylated metabolites produced from respective substrates.

### Summary of the data and conclusion

The findings of oligospermic men are summerized as follows;

1. elevated FSH and over-respons e of FSH; to LRH;
2. normal or elevated LH;
3. normal or low testosterone;
4. Leydig cells abundant or sparse;
5. Correlation between number of Leydig cell cluster and enzyme activity related to testosterone biosynthesis;
6. thickened tubular wall.

From the findings, it appears likely that the affected site of oligospermia is the testis itself.

Although the function of Sertoli cells remains

uninvestigated, several lesions in the testis of hyposermatogenesis might be suggested. Dysfunction of Leydig cells in some cases of olgiospermia would be present since low plasm testosterone inspite of increased Leydig cells with active steroidogeneis was observed. Some of testes with hypospermatogenesis revealed markedly thickened tubular wall. But it is difficult to decide whether the lesion is primary or secondary to elevated gonadotrophins.

The investigation of Sertoli cells would be of importance for further understanding of spermatogenesis.