INTRODUCTORY REMARKS: RUMINATIONS ON OVARIAN FUNCTION

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The opportunity to serve as the gadfly in residence for this meeting is an irresistible temptation. Without the usual editorial constraints, one can bare one's prejudices, fancies and even follies. I therefore propose to discuss selected aspects of follicular development in a series of mini-essays.

1. Development of primary follicles: LIFO, FIFO or chance:

Several years ago, when the specter of inflation first appeared, a number of corporations adopted new accounting procedures to handle their inventories. The acronyms then in vogue were FIFO and LIFO, standing for "first in, first out" and "last in, first out". These terms aptly apply to living as well as to corporate entities in describing the possible sequence of release of the products of endocrine and exocrine glands. For example, thyroglobulin fits the pattern of LIFO secretion since the most recently formed product is released preferentially on stimulation of the thyroid gland.

In considering the cues converting primordial to primary follicles, a hypothesis proposed by Edwards fits the FIFO model; i.e., the first formed oocytes are the first ones to be mobilized in the postnatal period. This is an interesting speculation but with no direct evidence - either pro or con. Pulse labelling of the prenatal ovary and subsequent autoradiographic studies at various times postnatally might indicate whether the maturation of oocytes is temporally programmed.

Alternatively, the recruitment of primordial follicles may represent a random process with chance proximity to blood vessels, nerves, more advanced follicles or corpora lutea (CL) acting as the signal for passage out of the resting pool.

The state of the art has at least advanced to the point where the problem is open to experimental attack. Trypsin-col-
lagenase digestion and subsequent culture of primordial follicles with peptide and/or steroid hormones, catecholamines, CL or more advanced follicles might yield interesting results.

2. **What stages of folliculogenesis are pituitary independent?**

The usual textbook account suggests that follicles can develop through the latest preantral stage before they fall under the influence of FSH and LH. In fact, a number of studies indicate that pituitary dependence begins at a much earlier stage in follicular development. For example, after hypophysectomy of the rat, mouse or hamster, the most advanced follicles fall far short of the normal 8-12 layered preantral stage. Moreover, in hypogonadotropic women, follicles are rarely encountered beyond the formation of 1 to 2 layers of granulosa cells.

In hypophysectomized hamsters and rats, replacement therapy with steroids and FSH and LH affects the number and histological appearance of small follicles. Similarly, in immature mice, deprivation of pituitary hormones also disrupts follicular development. Hence, there are quantitative and qualitative differences in preantral follicles in the absence of pituitary hormones. The concept of pituitary independence in early stages of folliculogenesis, therefore, seems to have little basis in fact.

3. **When does the follicle begin secreting estrogen?**

It is surprising that there is so little direct evidence on this point. It is axiomatic that the antral follicle is the principal source of the hormone - at least in non-primate species - but whether earlier preantral stages secrete estrogens for either local or distant consumption is unknown. At least in the hamster none of the enzymes involved in steroidogenesis can be localized by histochemical techniques in preantral follicles. In the rat, granulosa cells harvested from large preantral follicles and maintained in vitro, when supplied with androgen precursors, begin secreting estrogens after a lag period of 1-2 days. However, by this time these cells really may be physiologically comparable to antral granulosal cells. The methods are now available to resolve directly whether estrogen secretion is limited to the antral follicle. If this turns out to be true the interesting possibility then arises that younger follicles somehow tap the estrogen required for their further differentiation from more advanced follicles.

4. **An antral follicle is not an antral follicle.**

Detailed analysis of the antral follicle is now under way and for obvious reasons attention has focused on ripe follicles which are on the verge of ovulating. The obvious caveat is that the conclusions reached in analyzing mature antral follicles may not necessarily apply to younger stages. In its life history the tertiary follicle passes from infancy to maturity to senescence. Failure to keep this sequence in mind may account for some of the confusion on the steroidogenic capabilities of thecal and granulosa cells.