INTRODUCTION

The ovary has many similarities to other "renewal tissues" in adults. Renewal tissues are those in which differentiated, functional cells are continuously being replaced by proliferation of more primitive cells. These tissues are composed of a hierarchy of cells: at one end of the hierarchy are stem cells which are less differentiated and can divide without limit; at the other end are mature cells which are highly differentiated and have no capacity for proliferation (Mackillop et al., 1983). When a stem cell divides, each daughter cell has a choice: it can either remain a stem cell, or it can embark on a course of "clonal expansion" leading irreversibly to terminal differentiation (Fig 1). Daughter cells which embark on the second course are known as "transitional cells (Selby et al., 1983) or "committed progenitor cells" (Fitchen et al., 1981). Transitional cells have a limited capacity for cell division. They exhibit a continuous gradient of properties along a unidirectional vector; as cells move down the hierarchy, they acquire the differentiated features associated with specific tissue function, and they progressively lose the potential to divide (Mackillop et al., 1983). The more highly differentiated progeny greatly outnumber the less differentiated progenitor cells within the tissue.

In normal renewal tissues, cells are therefore arrayed along a maturation gradient. As cells progress down this gradient, they become more and more restricted in their developmental program. Although differentiated characteristics may not yet be expressed, transitional cells that are far removed from the parent stem cell are already committed to a particular differentiated fate. As cells progress down this gradient, their daughters multiply more and more rapidly (shorter generation time) but give rise to fewer and fewer subsequent generations (Lajtha, 1983).

The processes of growth and differentiation in transitional cells are regulated by a plethora of molecules. These regulatory molecules are stage-specific: each regulator acts on cells at a different stage along the maturation gradient (Sachs, 1986). It is likely that some of these
regulatory molecules are directive whereas others are permissive. Directive inductors convey information to a target cell, eliciting a specific developmental program from a choice of possibilities. Permissive inductors simply permit a particular tissue to continue its normal course of development (Cunha et al., 1983).

Key questions in understanding the processes of growth and differentiation in renewal tissues are:
1) What are the characteristics of transitional cells at various stages in the maturation gradient?
2) At what stages along this maturation gradient do transitional cells become progressively restricted in their developmental possibilities? When do they become irreversibly committed to a particular path of differentiation to the exclusion of all other possible outcomes?
3) What factors control the outcome at each of these branching points in the maturation pathway?
4) What induces stem cell progeny to begin a course of clonal expansion leading irreversibly towards terminal differentiation?
5) What regulates stem cell proliferation?

As in other renewal tissues, follicular development begins with a few, slowly dividing, less differentiated cells. As these cells increase in number, they begin to divide more rapidly; ultimately, cell division ceases and functional signs of differentiation appear. Normal follicles give rise to two possible end stage structures: secondary interstitium and corpora lutea. Some follicles become atretic, their granulosa cells undergoing dissolution and their theca cells differentiating into secondary interstitial gland (Erickson et al., 1985; Guraya and Greenwald, 1964, 1968). The interstitial gland persists for some time, but ultimately involutes. Other follicles ovulate, their granulosa and theca cells both differentiating into luteal cells. The corpus luteum functions for variable lengths of time and then undergoes regression. Thus, in either case, the follicle matures to form an end stage structure which performs its destined function and ultimately disintegrates to be replaced by proliferation of less differentiated cells.

The object of this paper is to characterize the maturation gradient in follicular development, to identify the branching points in the pathway, and to review what is known about the mechanisms which determine the outcome at these branching points. We conclude that most of our knowledge of follicular development is restricted to the penultimate and ultimate stages of this lengthy and complex process. The granulosa cells of large preovulatory follicles are about 10 generations removed from the pregranulosa cells of the primordial follicles from which they are descended. Nearly all studies of follicular development, in vivo and in vitro, focus on events that occur during the 8th, 9th and 10th generations. In contrast, the first 7 generations of follicular development remain largely unexplored.

For the most part, we will restrict our remarks to studies of the rat. The complex regulatory process which selects the appropriate number of follicles for ovulation is most fully expressed in the reproductively competent, adult, cycling rat. Many studies have been performed in prepubertal, infant, pregnant, or lactating rats. Recruitment and selection of ovulatory follicles does not take place in these animals, suggesting that certain regulatory mechanisms may not be operative. Therefore, while studies of other animal models have been extremely enlightening, caution must be used in extending conclusions to the cycling rat.