

## The human antral follicle : Functional correlates of growth and atresia

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**Summary.** This communication reviews the current information on the developmental relationships between the various tissues of the growing human antral follicle. It also examines the various interrelationships between the hormone levels in antral fluid, the populations of granulosa cells, the steroidogenic capacities of thecal tissue and granulosa cells, and the status of the oocyte in antral follicles at different stages of growth or degeneration.

Healthy antral follicles are considered to be those containing an oocyte which appears healthy at the level of the dissecting microscope and more than 50 p. 100 of its full complement of granulosa cells at each follicle diameter. In follicles with more than 75 p. 100 of their full complement of granulosa cells, at a given follicle diameter, the endocrine microenvironment is one that is enriched with FSH and oestradiol. Follicles with between 51 and 75 p. 100 of their full complement of granulosa cells at a given follicle diameter are invariably undergoing degenerative changes and their endocrine microenvironment is deficient in FSH and oestradiol but rich in androgen. However, it is believed that many of these follicles are still capable of being recruited back into the pool of healthy growing follicles. Atretic antral follicles are considered to be those undergoing irreversible degenerative changes: they usually contain < 50 p. 100 of their maximum number of granulosa cells and a degenerating oocyte. In atretic follicles, the endocrine microenvironment is deficient in FSH and oestradiol but contains levels of androstenedione comparable to those in healthy follicles.

The functional capacities of granulosa cells and thecal tissue from healthy follicles differ from those of atretic follicles. *In vitro*, granulosa cells from healthy follicles have the capacity to produce large amounts of oestradiol and smaller amounts of androstenedione and these estrogen-secreting cells retain the capacity to undergo mitosis in culture. By contrast, granulosa cells from atretic follicles do not have the capacity to produce much oestradiol although they remain steroidogenically competent for some time since they continue to synthesize androgens. *In vitro*, these cells are incapable of mitotic activity or of maintaining their population. *In vitro*, thecal tissue from both healthy and atretic follicles produces large amounts of androstenedione. In addition, thecal tissue from healthy but not atretic follicles produces some oestradiol.

The amount of degeneration of the oocyte *in vivo* and the subsequent maturational capabilities of the oocyte *in vitro* are correlated with the number of granulosa cells present and also with the levels of steroids in antral fluid. When healthy-looking oocytes were recovered from follicles with  $\leq$  50 p. 100 of their granulosa cells and/or had been exposed to high levels of androgen compared to oestrogen *in vivo*, their potential for meiotic maturation

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tion *in vitro* was severely reduced compared to oocytes from follicles with  $> 50$  p.100 of their full complement of granulosa cells and low androgen/œstrogen ratios.

It is suggested that the uninterrupted development of a human antral follicle is dependent upon its granulosa cells sustaining an œstrogen-enriched micro-environment within the follicle and its thecal envelope retaining the capacity to produce œstradiol as well as androstenedione.

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## **Introduction.**

A characteristic feature of the human ovary during the menstrual cycle is the presence of antral follicles in various stages of development or atresia. Of those antral follicles capable of further maturation, only one goes on to ovulate during each cycle. Most of the remaining antral follicles do not mature into ovulatory follicles but undergo degenerative changes at some earlier stage of their development. Despite the high incidence of follicular atresia in the human ovary relatively little is known about the functional status of follicles undergoing degenerative changes or how they differ from the population which have the potential for further development.

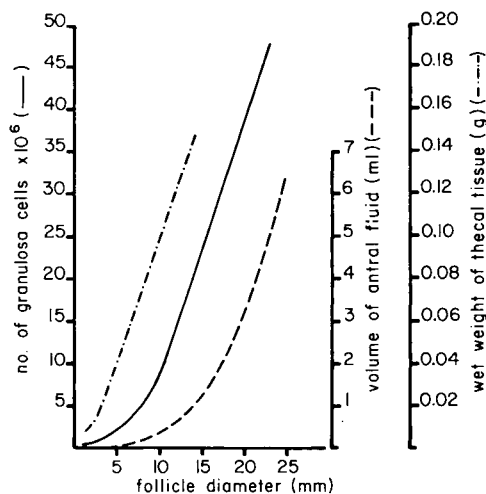
This communication reviews the current information on the developmental relationships between the various tissues of the developing human antral follicle. It then examines the various interrelationships between hormone levels in antral fluid, granulosa-cell numbers, the steroidogenic capacities of thecal tissue and granulosa cells, the status of the oocyte in antral follicles at different stages of growth or degeneration, and the potential of these oocytes for nuclear maturation *in vitro*. It is suggested that these data may help to provide a functional basis by which to assess the developmental status of the human antral follicle.

## **Developmental relationships between the various tissues of the growing human follicle.**

The non-growing primordial follicle in women is about 0.05 mm in diameter (Baker, 1963). It consists of a primary oocyte in prophase of the first meiotic division together with a single layer of spindle-shaped cells which are the undifferentiated granulosa cells. The oocyte-granulosa cell complex is separated from the surrounding stromal tissue by a basement membrane. Once this follicle starts to grow, its spindle-shaped granulosa cells become cuboidal and then undergo successive mitotic divisions. Coincident with granulosa-cell proliferation, fluid-filled spaces form between the cells. Also, at this time, some of the adjacent stromal cells outside the basement membrane become orientated in concentric perifollicular layers (for review see Ross and Vande Wiele, 1974). It has been suggested that the organization of the cells outside the follicle is regulated by the granulosa cells (Dubreuil, 1957). However, at present, there is no evidence to support this hypothesis. Just before antrum formation, the human follicle is about 0.2 mm in diameter and it contains 4 to 5 layers of granulosa cells. At this stage of follicular development the thecal compartment is about 0.02 mm in thickness. The cells of the thecal compartment are much less uniform in size compared to the membrana granulosa although some of them are comparable in diameter (i.e.,  $\sim 5$  to  $6 \mu\text{m}$ ). As the follicle enlarges beyond 0.2 mm, granulosa cells

continue to proliferate and the accumulating fluid in the extracellular spaces coalesce to form the antrum. Little is known about the speed with which this event takes place, however most follicles have a fully developed antrum by the time the follicle has reached a diameter of 0.4 mm. The organization of the granulosa cells in order to form the antrum appears to be regulated by FSH and oestradiol. In the hypophysectomized, immature female rat, addition of FSH alone does not stimulate follicular growth or antrum formation, whereas oestrogen alone induces granulosa cell proliferation without the formation of an antrum. Addition of FSH together with oestrogen induces granulosa cell proliferation together with the concurrent development of a fluid-filled antrum (Goldenberg *et al.*, 1972). In the human, the development of the follicle after antrum formation is associated with concomitant increases in its thecal-cell mass, granulosa-cell number and antral-fluid volume (fig. 1). When the human follicle has reached a diameter of  $\sim 4$  mm, its thecal envelope is about 0.12 mm in thickness and has an average wet weight of about 28 mg. In addition, some of the largest cells in this tissue have increased in diameter from 5 to 6  $\mu\text{m}$  to about 12  $\mu\text{m}$ . At this time, the follicle has accumulated about 1 million granulosa cells and about 30  $\mu\text{l}$  of antral fluid. Healthy follicles may continue to enlarge beyond 4 mm to reach a diameter of about 25 mm. There is insufficient information available on the thecal envelope of large follicles to draw conclusions about its properties. In two follicles, with a diameter of  $\geq 20$  mm, the thecal envelope averaged only about 0.15 mm in cross-section suggesting that this layer increases only slightly in thickness as the follicle enlarges from 4 mm to  $\geq 20$  mm. Nevertheless, the total mass of thecal tissue increases as the follicle develops beyond 4 mm in diameter (fig. 1). Some of the cells in

FIG. 1. — Relationship between follicle diameter, the maximum number of granulosa cells, and the average wet weight of thecal tissue at each follicle diameter.



the thecal envelope of large follicles ( $\geq 15$  mm diam.) increase in diameter to about 25  $\mu\text{m}$ . With the exception of the oocyte, these are the largest cells present in the follicle at this time. It appears that as the antral follicle develops, the thecal envelope increases in mass and some of its cells increase considerably in diameter. The tissue *per se*, however, apparently does not increase substantially in thickness. Within the basement membrane of the largest healthy antral-follicles, (i.e.,  $\geq 20$  mm in diame-

ter), there are between 40 and 50 million granulosa cells and up to 6.5 ml of antral fluid. The greatest accumulation of fluid occurs during the final stages of follicle maturation. For example, as the follicle increases in diameter from 20 mm to 25 mm the granulosa-cell number increases by 20 p. 100. During this time, however, its fluid volume increases by about 200 p. 100, i.e., from  $\sim 3.2$  ml to 6.5 ml (fig. 1). In large antral follicles, granulosa cells are much less uniform in size. Those cells closest to the basement membrane are larger than those nearest the follicular antrum. The largest granulosa cells are about 20  $\mu\text{m}$  in diameter which is close to the diameter of a luteal cell ( $\sim 25 \mu\text{m}$ ). Even some of the cells furthest away from the membrane are larger than they were at an earlier stage of development since their diameters may range up to 12  $\mu\text{m}$ . Thus, within the basement membrane of the enlarging antral follicle during its growth phase, there is a substantial increase in fluid volume, an overall increase in the size of many of the granulosa cells as well as an increase in the granulosa-cell number.

At the onset of the follicular phase, the largest human follicle with its full complement of granulosa cells, is about 4 mm in diameter. Such a follicle has increased 80-fold in diameter and accumulated about 1 million granulosa cells since it started to grow. Thus, the follicle which goes on to ovulate probably starts its growth long before the onset of the follicular phase in which it will ovulate. At the end of the follicular phase, the largest healthy follicle may reach a diameter of 25 mm. It is therefore apparent that the follicular phase of the menstrual cycle is associated with the relatively late stages of maturation of the ovulatory follicle. Indeed, the length of the follicular phase may be determined by the hormonal secretions from this follicle as it develops from a 4 mm structure to its final stage of maturation.

### **The endocrine microenvironment of healthy antral follicles.**

The endocrine microenvironment of a human antral follicle is profoundly influenced by the number of granulosa cells present (table 1). If a healthy antral follicle is defined as that follicle with a healthy-looking oocyte and with  $> 75$  p. 100 of the maximum number of granulosa cells possible for the diameter it has reached, the endocrine milieu of the antral fluid is characteristic for that type of follicle. It contains detectable levels of FSH ( $> 1.5$  mIU/ml) and high levels of  $\text{oestradiol}$  ( $> 1 \mu\text{g/ml}$ ) while androstenedione as well as progesterone, testosterone, dihydrotestosterone and  $\text{oestrone}$  are present at much lower concentrations (table 1 ; see McNatty and Baird, 1978 ; McNatty *et al.*, 1979a). Follicles might also be considered to be healthy, if they contain an oocyte that is not degenerating, and between 51 and 75 p. 100 of their full complement of granulosa cells per follicle diameter. However, these follicles no longer contain detectable levels of FSH and their levels of  $\text{oestradiol}$  have declined sharply while those of androstenedione remain unchanged. Although these follicles no longer have an  $\text{oestrogenic}$  microenvironment, their granulosa cells can be stimulated *in vitro* to aromatise androstenedione to  $\text{oestradiol}$  in the presence of FSH (McNatty, unpublished data). Presumably therefore, some of these follicles could be rescued from further degeneration and recruited back into the pool of healthy growing follicles when stimulated with a gonadotrophin preparation rich in FSH-activity.

TABLE 1

Interrelationships between the number of granulosa cells, the concentrations of FSH\* and steroids in antral fluid and the status of the oocyte in human follicles

Number of granulosa cells per follicle ( $\geq 1$ mm diam.)	$\times 100$	Number of observations	Concentration of FSH* and steroids in antral fluid (mean $\pm 1$ SEM)		$\Delta_4/E_2$	p. 100 Oocytes at each stage of maturation <i>in vivo</i>				
			FSH(n) mIU/ml	$\Delta_4$ ng/ml		$E_2$ ng/ml	Healthy GV	Degenerating GV	GVBD	Necrotic
$\geq 95$		8	3.6 $\pm 0.6$ (7)	807 $\pm 194$	1 658 $\pm 410$	0.76 $\pm 0.18$	75.0	12.5	12.5	—
76-100		12	2.7 $\pm 0.4$ (8)	835 $\pm 241$	1 158 $\pm 343$	4.70 $\pm 2.17$	66.7	16.7	8.3	8.3
51-75		11	< 1.5 (6)	1 053 $\pm 218$	94 $\pm 29$	26.67 $\pm 9.47$	72.7	27.3	—	—
26-50		37	< 1.5 (15)	906 $\pm 143$	189 $\pm 86$	26.53 $\pm 4.10$	48.7	45.9	2.7	2.7
0-25		24	< 1.5 (12)	864 $\pm 236$	58 $\pm 20$	64.40 $\pm 18.90$	25.0	62.5	4.2	8.3

Follicles examined were all  $\geq 1$  mm diameter.

\* FSH was not assayed in all follicles since insufficient fluid remained in some cases after the steroids were assayed; n = number of FSH assays.  
 $\Delta_4$  = androstenedione,  $E_2$  = oestradiol, GV = oocyte with germinal vesicle, GVBD = germinal vesicle breakdown with or without polar body formation.

In summary, the endocrine microenvironment of the healthiest antral follicle is one which is enriched with FSH and oestrogen and has the lowest levels of androgen. A progressive reduction in the number of granulosa cells is associated with a simultaneous reduction in the level of oestrogen and FSH and with a reduced probability of recovering a morphologically normal-looking oocyte or of recovering one that is likely to complete the process of nuclear maturation *in vitro*.

### **The endocrine microenvironment in atretic follicles.**

An antral follicle may be considered to be undergoing irreversible degenerative changes when it has less than 50 p. 100 of its full complement of granulosa cells. Many of the healthy-looking oocytes from these follicles, when cultured, are unable to resume meiosis (McNatty *et al.*, 1979a). Moreover, in these follicles, the level of oestradiol is less than 20 p. 100 of that in follicles with their full complement of granulosa cells and the level of androgen is many-fold higher than that of oestrogen (table 1). Also, granulosa cells from many of these degenerating follicles are incapable of metabolizing androstenedione to oestradiol when exposed to FSH (McNatty, unpublished data). Therefore, these follicles are unlikely to recover from their degenerative state since they no longer have cells with the capacity to enrich the follicular microenvironment with oestrogen (McNatty and Baird, 1978).

Irrespective of the criteria used to assess follicular atresia, most follicles which show degenerative changes still contain high levels of steroid similar to the levels in healthy follicles (table 1). However, degenerating follicles invariably have low levels of oestrogen and FSH and a level of androgen which exceeds that of oestrogen.

### **Steroid production by thecal tissues and granulosa cells from healthy and atretic antral follicles.**

In tissue culture, both granulosa cells and thecal tissues from human follicles have the capacity to produce progestins, androgens and oestrogens (McNatty *et al.*, 1979b). However, the pattern of steroid production by the two cell-types differ (figs. 2a, b). Moreover, even for each cell-type, the pattern of steroids produced differs according to whether the cells or tissues were harvested from healthy follicles ( $> 50$  p. 100 of their maximum number of granulosa cells) or atretic follicles ( $\leq 50$  p. 100 of their maximum number of granulosa cells) (figs. 2a, b).

Granulosa cells from healthy follicles, irrespective of follicle-size or stage of cycle, produce *de novo* 5- to 100-times more oestrogen than that produced by cells from atretic follicles. Moreover, they produce more oestradiol than androstenedione. It seems that throughout most stages of antral follicle growth, granulosa cells have the capacity for *de novo* synthesis of oestradiol. By contrast, during follicular atresia, granulosa cells lose their capacity to synthesize oestrogen but not androgen. They therefore dedifferentiate from an oestrogenic state into an androgenic one.

Irrespective of the developmental status of the follicle, granulosa cells are incapable of producing very much progesterone *in vitro* unless the cells are recovered from a healthy follicle during the late follicular phase (fig. 2a). These enlarged cells show

morphological characteristics similar to those of luteal cells and they are fully competent to secrete progesterone in response to LH stimulation (Baird *et al.*, 1975 ; McNatty, 1979).

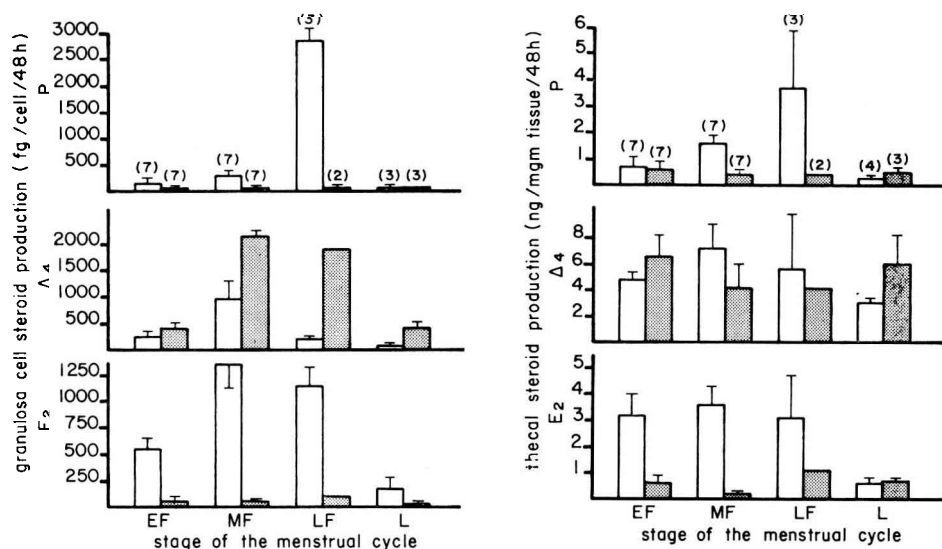


FIG. 2. — The production of progesterone, androstenedione, and oestradiol by granulosa cells (fig. 2a) and thecal tissue (fig. 2b) harvested from healthy and atretic follicles at different stages of the menstrual cycle. Data for healthy follicles is shown by the white histograms. Data for atretic follicles is shown by the black histograms. Healthy follicles were those containing > 50 p. 100 of their maximum granulosa-cell number. Atretic follicles were those containing < 50 p. 100 of their maximum granulosa-cell number. Hormone production was that amount accumulated in the culture medium after 48 h culture minus the amount presented in the tissue and medium at the start of culture. EF, MF LF refer to early, mid — and late follicular phase while L refers to luteal phase. All values are expressed by means  $\pm$  1 SEM.

Throughout most stages of antral follicle development it seems that granulosa cells may be present in one of two functionally differentiated states. The functional status of granulosa cells determines whether the endocrine microenvironment of the follicle is « oestrogenic » or « androgenic » since these cells account for about 90 p. 100 of the oestradiol and between 30 and 80 p. 100 of the androgen in antral fluid (McNatty and Baird, 1978 ; McNatty *et al.*, 1979c). Moreover, the functional status of granulosa cells influences their level of mitotic activity. A granulosa cell suspension with the capacity to enrich its *in vitro* environment with oestrogen increases its population during culture. By contrast, a granulosa cell suspension with the capacity to enrich its *in vitro* environment with androgen is unable to increase its cell number or even maintain its existing population during long-term culture (McNatty *et al.*, 1979b).

Thecal tissue *in vitro* is primarily a source of androstenedione and to a lesser extent of oestradiol. The capacity of thecal tissue from healthy follicles to produce androstenedione is comparable to that from atretic follicles. The functional capacity

of thecal tissue in healthy follicles differs from that in atretic follicles in its capacity to produce oestrogen: thecal tissue from healthy follicles produces relatively large amounts of oestradiol compared to that produced by tissue from atretic follicles (fig. 2*b*).

It would seem that a healthy follicle is one which contains granulosa cells with the *de novo* capacity to produce oestradiol and a thecal envelope with the capacity to produce oestradiol as well as androstenedione. Furthermore, it is suggested that a follicle in its irreversible stages of atresia is one which contains both granulosa cells and thecal tissue with the capacity to produce androgens but not oestrogens.

### The relationship between hormone levels in antral fluid and oocyte maturation *in vivo* and *in vitro*.

The hormonal milieu of antral fluid is correlated with the viability of the oocyte *in vivo* (table 1). Morphologically normal oocytes with a germinal vesicle were most frequently obtained from follicles with a high level of oestradiol or were presumed to have recently had high levels of this hormone in antral fluid (table 1). By contrast, degenerating oocytes were more frequently obtained from follicles which had been « androgenic » for some period of time. It seems that the amount of oocyte degeneration is dependent on both the number and the functional status of its adjacent granulosa cells. Apparently, the oocyte is not threatened until the level of oestrogen has been about 25-fold lower than that of androgen for a certain period of time. This degree of androgen exposure occurs after the follicle has lost more than 50 p. 100 of its granulosa cells. In the majority of follicles, it appears that functional changes in the

TABLE 2

*Relationships between the ability of human oocytes \* to resume meiosis in vitro, the size of the oocyte and the concentrations of androstenedione and oestradiol in antral fluid*

Oocyte status after 48 hrs in culture	Number of observations n (n <sup>1</sup> )	Oocyte diameter (μm)	Steroid concentration in antral fluid (ng/ml)		
			Androstenedione (Δ <sub>4</sub> )	Oestradiol (E <sub>2</sub> )	Δ <sub>4</sub> /E <sub>2</sub>
GV	14 (19)	108.2 (a) ± 0.9	825 ± 220	106 b ± 79	11 (d) ± 3
GVBD	11 (14)	110.6 ± 2.3	1 183 ± 320	87 (c) ± 31	40 (de) ± 13
PB	11 (10)	117.2 (a) ± 2.2	876 ± 178	1 019 (bc) ± 300	11 (e) ± 5
Necrotic	1(2)	95.5 ± 4.5	473	12	39

(\*) Data presented is for germinal vesicle stage oocytes which appeared free of degeneration at the level of the dissecting microscope (× 100). All values are expressed as means or means ± SEM. GV = oocyte with germinal vesicle, GVBD = oocyte that underwent germinal vesicle breakdown but did not form a polar body, PB = oocyte with polar body, n = number of steroid measurements, n<sup>1</sup> = number of oocyte measurements, a, b, c, d, e = all p < 0.02.



steroidogenic capacity of granulosa cells and/or thecal tissue normally precede any visible degenerative changes in the oocyte (McNatty *et al.*, 1979a).

Only 53 p. 100 of the oocytes that appeared free of degeneration *in vivo* were capable of resuming meiosis and/or completing the first meiotic division *in vitro* (table 2). The behaviour of healthy-looking oocytes *in vitro* was correlated with their diameter and the level of oestradiol and androstenedione in antral fluid (table 2). Provided the oocyte had a diameter ranging between 115-120  $\mu\text{m}$  and was bathed in a fluid with high oestrogen levels relative to those of androgen, it was capable of resuming meiosis and forming a polar body after being removed from the follicular environment and cultured for 48 hrs. By contrast, oocytes not significantly different in diameter (108-113  $\mu\text{m}$ ) which were bathed in a fluid, with low oestrogen levels relative to androgen, were capable of undergoing germinal vesicle breakdown but not forming a polar body *in vitro* (table 2). Oocytes significantly smaller (107-109  $\mu\text{m}$ ) than those which formed polar bodies but exposed to the same androgen/oestrogen ratio ( $\Delta_4/\text{E}_2 = 11$ ) were unable to resume meiosis and retained their nuclei throughout the culture period. Two oocytes harvested from a highly-androgenic fluid environment were unable to recover *in vitro* and underwent necrotic changes.

Little is known concerning the regulation of oocyte maturation within the developing follicle. The present results indicate that the oocyte must grow to a certain diameter before it is competent to undergo nuclear maturation. These data confirm, in the human, the correlation between oocyte diameter and capacity to resume meiosis described for hamsters (Iwamatsu and Yanagimachi, 1975) and mice (Sorensen and Wassarman, 1976). The present data also show that a follicular environment relatively rich in oestrogen is required to maintain the oocyte in a morphologically normal condition and to permit the healthy-looking, fully-grown germinal vesicle-stage oocyte to undergo nuclear maturation in culture. These results are in agreement with Hunter, Cook and Baker (1976) for pigs, Moor (1978) for sheep, Smith, Conaway and Kerber (1978) for rhesus monkeys and Smith and Tenney (1978) for hypophysectomized mice.

It has also been suggested that a non-steroidal substance in antral fluid of several species, including man, prevents the oocyte from resuming meiosis *in vivo* before the ovulatory LH surge (Channing and Tsafiriri, 1978 ; Tsafiriri, Pomerantz and Channing, 1976 ; Hillensjö *et al.*, 1978). If this were the only factor important in regulating the resumption of meiosis, the removal of similar-sized human oocytes from their follicular environment should have resulted in similar rates of polar body formation *in vitro* regardless of the steroid concentration in the antral fluid. The present data, and those of others, suggest that oocytes from follicles with the highest concentrations of oestrogens relative to androgens have the greatest potential for nuclear maturation in culture. Thus, nuclear maturation *in vivo* is probably not turned off or on simply by the presence or absence of a protein inhibitor but is likely to be much more finely tuned by the endocrine status of the follicle cells before the LH stimulation of the resumption of meiosis in preovulatory oocytes.

## Conclusions.

The development of the human antral follicle is associated with concomitant increases in the mass of its thecal envelope, in the number of its granulosa cells and in

its antral-fluid volume. Also during development, the steroid-producing cell-types of the follicle, undergo varying degrees of enlargement. During follicle growth, the mitotic activity of granulosa cells and the viability of the oocyte are dependent upon the granulosa cells retaining their capacity to enrich the follicular microenvironment with œstrogen. The cells are only able to maintain this functional status if FSH is present within the follicle. In the absence of FSH, granulosa cells lose their capacity to produce œstrogen and they dedifferentiate into functionally competent androgen-secreting cells. This loss in aromatase activity by granulosa cells is associated with a similar loss in the thecal tissues.

At the same time oocytes undergo a reduction in maturational capacity or begin to degenerate. Therefore, the uninterrupted development of a human antral follicle appears to be critically dependent on the presence of FSH in antral fluid and on the thecal and granulosa cells retaining the capacity to produce œstradiol.

*EEC Seminar on « Ovarian stimulation and egg quality in mammals », Luynes, France, octobre 1978.*

**Acknowledgements.** — We wish to thank Ms. Roberta Todd for measuring FSH in antral fluid and Dr. Anastasia Makris and Mr. Camillio de Grazia for assisting with the steroid assays in culture media and human antral fluid. We also wish to thank Ms. Denise Lung for the typing of this manuscript. Dr. K. P. McNatty is a recipient of a Harkness Fellowship from the Commonwealth Fund of New York. This research was supported by Public Health Service Grants Nos HD06916, HD07923, HD06645.

**Résumé.** Ce rapport analyse les informations actuelles relatives à l'interaction des divers tissus du follicule antral humain au cours de son développement. Il examine également les diverses corrélations qui existent entre les taux d'hormones dans le fluide folliculaire, les populations de cellules de la granulosa, les capacités stéroïdogènes du tissu thécal et des cellules de la granulosa, ainsi que l'état de développement de l'ovocyte à chaque étape de la croissance ou de la dégénérescence des follicules à antrum.

Le bon état des follicules à antrum est jugé d'après l'état de leur ovocyte et par la présence de plus de 50 p. 100 du nombre normal de cellules de la granulosa pour chaque taille folliculaire. Pour les follicules renfermant plus de 75 p. 100 du nombre normal de cellules de la granulosa, le micro-milieu endocrinien est riche en FSH et en œstradiol. Les follicules contenant de 51 à 75 p. 100 de leur nombre final de cellules de la granulosa sont normalement destinés à dégénérer et leur micro-milieu endocrinien est appauvri en FSH et en œstradiol, mais riche en androgènes. Il semble cependant que beaucoup de ces follicules puissent encore être réintroduits dans le pool des follicules sains en croissance. Sont considérés comme follicules antraux atrétiques ceux qui subissent des changements dégénératifs irréversibles : ils renferment généralement moins de 50 p. 100 de leur taux maximal de cellules de la granulosa et possèdent un ovocyte dégénéré. Le micro-milieu endocrinien de ces follicules atrétiques est pauvre en FSH et en œstradiol, mais contient des taux d'androstènedione comparables à ceux des follicules non atrétiques.

Les capacités fonctionnelles des cellules de la granulosa et du tissu thécal des follicules sains diffèrent de celles des follicules atrétiques. *In vitro* les cellules de la granulosa des follicules sains peuvent produire de grandes quantités d'œstradiol et des quantités moindres d'androstènedione : *in vitro* ces cellules sécrétrices d'œstrogène peuvent se diviser en culture. Au contraire, les cellules de la granulosa des follicules atrétiques ne peuvent produire une grande quantité d'œstradiol, bien qu'elles conservent leur aptitude stéroïdogène pendant un certain temps, puisqu'elles synthétisent des androgènes. *In vitro* ces cellules n'ont

plus d'activité mitotique et leur nombre décroît. *In vitro* le tissu thécal provenant des follicules atrétiques ou non, fabriquent de grandes quantités d'androstènedione. Seul le tissu thécal provenant de follicules non atrétiques produit de l'œstradiol.

La résistance de l'ovocyte *in vivo* et sa capacité à effectuer sa maturation *in vitro* dépendent du nombre de cellules de la granulosa présentes dans le follicule ainsi que des taux de stéroïdes folliculaires. Des ovocytes apparemment sains, mais provenant de follicules contenant moins de 50 p. 100 du nombre normal de cellules de la granulosa et/ou qui ont été exposés *in vivo* à des taux élevés d'androgènes et de faibles taux relatifs d'œstrogène, s'avèrent incapables de reprendre leur méiose *in vitro* et de former leur globule polaire à un taux comparable à celui d'ovocytes provenant de follicules contenant plus de 50 p. 100 de la population normale de cellules de la granulosa et soumis à un faible rapport androgènes/œstrogènes.

Nous suggérons que, pour qu'un follicule à antrum humain se développe de manière ininterrompue, les cellules de la granulosa doivent maintenir un micro-milieu intrafolliculaire riche en œstrogène et la thèque doit être capable de produire de l'œstradiol en même temps que de l'androstènedione.

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