THE INFLUENCE OF THE SUPRARENAL CORTEX ON THE GONADS OF RABBITS.

I. The Effects of Suprarenal Injury (by Removal or Freezing) on the Interstitial Cells of the Ovary.

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INTRODUCTION.

It is well known that hypertrophic changes occur in the interstitial cells of the ovary, and in the suprarenal cortex, in certain animals during pregnancy. Likewise, investigators are in general agreement that removal of the gonads causes hypertrophy of the suprarenal cortex. With these facts in mind, it occurred to us that conversely suprarenal injury might produce changes in the sex glands. We therefore studied the data of nearly 400 rabbits that had been subjected to various types of suprarenal injury. In the present communication the details of the observations on the changes which take place in the ovary following suprarenal injury are reported. Brief references to certain of these changes have already been made by one of us (1, 2) in other publications.

LITERATURE.

While the literature contains several references dealing directly with the effects of gonadectomy and pregnancy on the suprarenal cortex, there seem to be no references dealing particularly with the effects of suprarenalectomy on the gonads and only a few in which such a relation is considered at all.

Novak (3) studied the effects of suprarenalectomy on the genital tracts of male and female white rats. The animals survived the operation, done in two stages, from several days to several months. He noted that suprarenal extirpa-

tion caused hypoplasia or atrophy of the genital tract. He did not study particularly the effects on the interstitial cells either of the testis or of the ovary.

Cesa-Bianchi (4) described fatty degeneration of the interstitial cells of the ovary occurring in guinea pigs which survived double suprarenalectomy for from 2 to 4 days, but the functional significance of such changes in lipoid-rich cells and especially when occurring in moribund animals is doubtful. Likewise the observation of Sserdjukoff (5) on four pregnant cats, all of which died within 3 days after suprarenalectomy and in which an increase was found in the size of the interstitial and lutein cells, is open to the severe criticisms that only four animals were used; that pregnancy normally induces hypertrophy of the interstitial cells; and that animals moribund from the time of operation could show hypertrophic changes ascribable to suprarenal insufficiency. Pende (6), working with cats, also reported an increase in the interstitial cells of the ovary following suprarenalectomy. But Elliott (7) reports that he did not observe any significant changes in the ovaries or testes of cats following partial or double suprarenalectomy.

On the other hand, there are many observations showing that gonadectomy causes enlargement of the suprarenal cortex in rabbits, guinea pigs, and dogs (Theodossieff (8), Schenk (9), and Kolde (10)), although Elliott (7) was unable to detect any enlargement of the suprarenal glands in twelve gonadectomized cats. Likewise, many observers have noted the enlargement of the cortex in pregnancy (Guieysse (11), Kolmer (12), Kolde (10), and Schenk (9)).

Riddle (13) recently reported enlargement of the suprarenals in pigeons during ovulation.

Embryology.

The interstitial cells of the ovary were first described by Pflüger in 1863, but His (14) in 1865 was the first to describe them in detail in the ovary of the cat and to discuss their possible significance. Their occurrence in close association with the spindle-shaped stroma cells, and in apparently close association with the blood capillary network led him to regard them as developed from stroma cells, but he also suggested that they might arise from cells embryologically related to blood capillaries.

An association of the interstitial cells with the theca interna of follicles was described almost from the time of their first observation. His believed that the interstitial cells gave rise to the theca interna, while more recent investigators have claimed that the interstitial cells were derived from the theca interna cells of the immature follicles undergoing regression or atresia (von Koelliker (15), Allen (16), Fellner (17), and Kingsbury (18)).

Other modes of origin of the interstitial cells have been advanced. Lane-Claypon (19) contends that in the rabbit ovary they are derived from the germinal epithelium as cell cords in common with the ova, and that the interstitial cells remain grouped together in spaces between the follicles instead of arranging themselves around developing ova. She also believes that ova may be formed

from interstitial cells and that this actually begins to take place in the maternal ovary on about the 20th day of pregnancy.

We have briefly stated the two principal views concerning the origin of the interstitial cells of the ovary, and it is interesting to note in this connection that there are similarly two principal views regarding the origin of the interstitial cells of the testes: (1) that they are connective tissue cells, and (2) that they are epithelial cells derived from the germinal epithelium.

The relation between the interstitial and lutein cells is found in the view more or less definitely expressed by many workers that no fundamental differences exist between the regressive changes that occur in corpora lutea and those occurring in unruptured follicles undergoing degeneration. Schulin (20) was among the first to express this view, and he believed that he detected intermediate forms between typical atresia of the follicles and corpus luteum formation. Many others have expressed their belief in the fundamental similarity of the two processes.

Allen, who believes in the connective tissue origin of the interstitial cells, states that the interstitial and lutein cells look so much alike that it seems improbable that two groups of cells morphologically identical could have arisen from such diverse elements as connective tissue of the theca interna on the one hand, and granulosa cells on the other. He favors a common origin for these two groups of cells, believing with Clark (21), Van Beneden (22), and von Koelliker that the lutein cells and interstitial cells arise from the theca interna. Others, who accept the common origin of the interstitial and lutein cells, believe, however, that they both arise from germinal epithelium. Van der Stricht (23), working with the bat, found that both granulosa and interstitial cells of the theca interna take part in the formation of the corpus luteum. However, the similarity of the structures arising from both ruptured and unruptured follicles and the embryological relation between the interstitial and lutein cells is emphatically denied by many, particularly Sabotta (24).

The significance of the common origin of these different ovarian elements becomes more apparent when the views regarding the functional importance of these cells are considered. The conception of a common origin of follicle and interstitial cells permits of a functional association between interstitial and lutein cells. It allows a satisfactory answer to the perplexing fact that interstitial cells have not been definitely found in many species. Even in the human ovary, while they have been apparently demonstrated by some workers, their existence has been questioned by others. In any event, they are few in number and require a special technique for demonstration.

This brief summary of the conflicting views concerning the relation between interstitial and lutein cells indicates that anatomical studies must be combined with carefully planned physiological and chemical studies in order to determine whether the lutein cells and interstitial

cells have a common origin either from the germinal epithelium or from the connective tissue, or whether the lutein cells arise from one type of tissue and the interstitial cells from the other.

Histology.

The interstitial cells of the rabbit ovary are large polyhedral cells about 15 micra in diameter. The nucleus is large, vesicular, and distinctly polychromatic, while the cytoplasm is crowded with droplets of lipoid substance. The chemical composition of the lipoid substances has not been definitely determined, but like the lipoids of the suprarenals they contain cholesterol and lecithin. Cowdry (25) could not confirm the observations that the mitochondria exhibit special peculiarities. The reticular apparatus has been carefully studied without bringing to light any special distinctive features. Pigments other than lipochrome are of rare occurrence.

A number of writers have spoken of the interstitial cells of the ovary as the interstitial gland. Bouin (26) and Limon (27) were among the first to do so. The view is based largely on morphological studies of the interstitial cells in the rabbit and bat. Interstitial cells are present in varying numbers in different animals. They are present in large numbers in the rabbit, bat, and cat ovaries, scantily developed in the human ovary, and up to the present time have not been demonstrated in the pig, sheep, and cow.

Presentation of Data.

This report is based on a study of the clinical and necropsy protocols of thirty rabbits that were subjected to double suprarenalectomy, and of thirteen rabbits in which the suprarenals were injured by partial removal or by freezing.[1] All animals were sexually mature at the time of death. The principal data of these two groups have been collected in Tables I and II and arranged according to the duration of life after suprarenalectomy or injury.

Double Suprarenalectomy.—Examination of Table I shows that bilaterally suprarenalectomized rabbits which survive the operation for several weeks frequently show enlargement of the ovaries, while

[1] All operations were performed under ether anesthesia.

those succumbing within 2 weeks generally do not. A survival period of 30 days has been taken arbitrarily as sufficient time in which cellular changes or compensatory hypertrophy would manifest themselves.

Thirteen animals survived the operation for less than 30 days and of those, ten, or 77 per cent, showed small, normal sized ovaries, with no significant hypertrophy of the interstitial cells. Three, or 23 per cent, presented enlarged ovaries. These three (Nos. 8, 12, and 13) survived double suprarenalectomy for 17, 24, and 27 days respectively and died with symptoms of suprarenal insufficiency.

Of the seventeen rabbits which survived double suprarenalectomy for more than 30 days, four, or 24 per cent, showed no ovarian enlargement, eight, or 47 per cent, showed moderately enlarged ovaries (about twice normal size), while five, or 29 per cent, showed markedly hypertrophied ovaries (about three times normal size). The enlargement consists essentially of an hypertrophy of the interstitial cells. The enlarged cells frequently measure 30 micra in diameter. They become very fatty and often take on a radial arrangement similar to that seen in the suprarenal cortex. That there exists a striking general relationship between the degree and frequency of ovarian hypertrophy and the duration of life after suprarenalectomy is shown by the fact that six of the seven animals surviving over 60 days showed ovarian enlargement, while seven of the ten surviving between 30 and 60 days showed enlargement, and only three of the thirteen surviving less than 30 days showed enlargement.

Further analysis of the data shows that, in addition to the relation between the duration of life and the degree of ovarian hypertrophy, there is a general parellelism between the amount of accessory suprarenal tissue found at autopsy and the degree of ovarian enlargement. In the first instance, this adds further data that survival after double suprarenalectomy depends on the presence of accessory suprarenal cortex, and secondly, it suggests that both the hypertrophy of the accessory cortical tissue and that of the interstitial cells of the ovary are compensatory and brought about in part at least by the same mechanism.

Partial Suprarenalectomy.—The effects on the ovaries of partial suprarenalectomy by removal or freezing have been studied in thirteen rabbits. The data relative to these are given in Table II. In twelve

TABLE I.

Double Suprarenalectomy.

Rabbit No.	Interval between removal of right and left suprarenals.	Major cause of death.	Interval between suprarenalectomy and examination of ovaries.	Fragments or accessory suprarenals.	Size of ovaries.	Interstitial cells.	Interval between last pregnancy and examination of ovaries.	Corpora lutea.
	days		*days*				*days*	
1	7	Pneumonia.	1	None found.	Normal.	Normal.	60	
2	12	Suprarenal insufficiency; infected right suprarenalectomy wound.	2	" "	"	"	213	
3	148	Suprarenal insufficiency.	2	One accessory.	"	"		
4	0	Pneumonia; snuffles.	2	Two 1 mm. accessories.	"	"		
5	0	"	2	None found.	"	"		
6	14	Suprarenal insufficiency; wound infection.	7	" "	"	"		
7	9	Suprarenal insufficiency.	10	" "	"	Moderately hypertrophic.		
8	215	" "	17	" "	Markedly enlarged.	Markedly hypertrophic.		
9	95	" "	17	One small accessory.	Normal.	Normal.		Few small groups of lutein cells.
10	25	Snuffles; suprarenal insufficiency	17	None found.	"	"		

11	37	Pneumonia.	20	One small accessory.	Normal.	Moderately hypertrophic.		
12	0	Sacrificed.	24	None found.	Markedly enlarged.	Markedly hypertrophic.		
13	37	Suprarenal insufficiency.	27	" "	Moderately enlarged.	Moderately hypertrophic.	80	
14	7	" " respiratory infection.	30	Six small accessories.	Moderately enlarged.	Moderately hypertrophic.		
15	7	Suprarenal insufficiency.	30	Two small accessories.	Moderately enlarged.	Moderately hypertrophic.		
16	68	" " hastened by anesthetic.	30	One minute accessory.	Markedly enlarged.	Markedly hypertrophic.		Several large corpora lutea; uterus normal; mammary gland hypertrophic.
17	0	Abscess in neck; sacrificed.	32	None found.	Normal.	Normal.		Few small groups of lutein cells.
18	143	Arsenic poisoning.	34	" "	"	"	195	
19	7	Died after exploratory operation.	35	Two small accessories; one fragment 1.5 by 1 mm.	"	"		
20	75	Empyema.	40	Two small accessories.	Moderately enlarged.	Markedly hypertrophic.		
21	32	Suprarenal insufficiency.	42	None found.	Markedly enlarged.	Markedly hypertrophic.		
22	68	Snuffles; sacrificed.	43	One 0.5 mm. stump on left; one 4 by 3 mm. stump on right; one small accessory.	Moderately enlarged.	Moderately hypertrophic.		
23	21	Suprarenal insufficiency.	47	Three small accessories.	Moderately enlarged.	Markedly hypertrophic.		

TABLE I—*Concluded.*

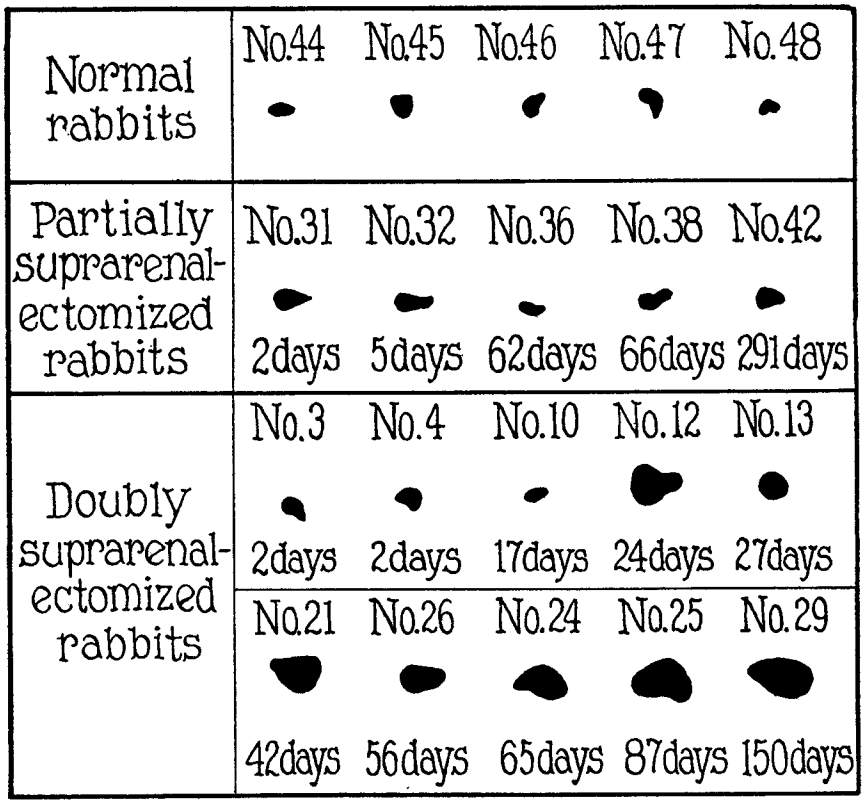
Rabbit No.	Interval between removal of right and left suprarenals.	Major cause of death.	Interval between supra-renal-ectomy and examination of ovaries.	Fragments or accessory suprarenals.	Size of ovaries.	Interstitial cells.	Interval between last pregnancy and examination of ovaries.	Corpora lutea.
	days		*days*				*days*	
24	180	Subcutaneous abscesses; bronchopneumonia; sacrificed.	65	Mass of hyperplastic cortex with some medulla on right.	Markedly enlarged.	Markedly hypertrophic.		Few small groups of lutein cells.
25	6	Sacrificed to terminate experiment.	87	One large accessory 5 by 2.5 mm.	Markedly enlarged.	Markedly hypertrophic.		
26	6	Sacrificed to terminate experiment.	88	One very large accessory.	Moderately enlarged.	Moderately hypertrophic.	53	
27	21	Strong and healthy; sacrificed.	102	Three small accessories.	Normal.	Normal.		
28	0	Moribund; sacrificed.	143	One very large accessory.	Moderately enlarged.	Markedly hypertrophic.		
29	25	Intravenous injection of vaccine.	150	Two small accessories.	Markedly enlarged.	Markedly hypertrophic.		Several large corpora lutea; uterus normal; mammary gland hypertrophic.
30	100	Suprarenal insufficiency.	150	One small accessory.	Moderately enlarged.	Markedly hypertrophic.	36	

TABLE II.

Partial Suprarenalectomy.

Rabbit No.	Major cause of death.	Interval between suprarenalectomy and examination of ovaries.	Size of ovaries.	Interstitial cells.	Interval between last pregnancy and examination of ovaries.	Corpora lutea.
		days			*days*	
31	Snuffles; chronic pneumonia.	2	Normal.	Normal.	256	
32	Anesthetic.	5	"	Moderately hypertrophic.		
33	Infection of wound.	8	"	Normal.	138	
34	Extreme emaciation, mange, and right purulent pleurisy; sacrificed.	11	"	"	190	Several small groups of lutein cells.
35	Killed by accident.	47	"	"		
36	Pneumonia.	62	"	"		
37	?	65	"	"		
38	Sacrificed.	66	"	"		
39	Marked emaciation; weakness; sacrificed.	150	"	"	153	
40	Mange and weakness; sacrificed.	159	"	"	127	
41	" arsenic poisoning.	174	"	"	199	Few small groups of lutein cells.
42	Myxedema; mange; sacrificed.	291	"	"		
43	Paralysis of hind legs; peritonitis.	1,095	Markedly enlarged.	"	532	

the ovaries were of average normal size, and the interstitial cells generally showed no recognizable differences from those seen in normal rabbits. In one very old animal (No. 43) known to have been pregnant four times, the ovaries were much enlarged. The interstitial cells, however, were not prominent, and the enlargement was found to be due to a considerable increase in the stroma tissue.



TEXT-FIG. 1. Tracings of representative cross-sections of ovaries of normal rabbits, partially suprarenalectomized rabbits, and doubly suprarenalectomized rabbits, showing the relation of ovarian hypertrophy to duration of life after suprarenalectomy.

As this study was incidental to the main purpose for which these rabbits were originally used, the weights of the ovaries were not recorded. All autopsies were made by one of us, and in most instances

transverse sections were taken from the middle third of the ovary for microscopic study. Formalin fixation, celloidin embedding, and hematoxylin and eosin staining were used in all. Tracings of the actual size of cross-sections of the ovaries are given in Text-fig. 1. These are arranged to show the size of the normal ovary and the size of the ovary after partial and after double suprarenalectomy in relation to duration of life.

Three of the rabbits, though not pregnant, were found to have large corpora lutea, similar in all respects to those of pregnancy. This observation raises several important questions in relation to ovulation in rabbits (28) and the influence of suprarenalectomy on corpus luteum production, which will be dealt with in a separate paper.

Nineteen additional experiments in which double or partial suprarenalectomy was complicated with pregnancy were not included in the present report.

The work of previous observers was confirmed in that no evidence of variation in the size or structure of the ovary dependent upon season or rut was found (29).

DISCUSSION.

Data have been presented concerning thirty rabbits that were subjected to double suprarenalectomy, and thirteen in which the suprarenals were injured by partial removal or by freezing. Of the seventeen animals surviving double suprarenalectomy for over 30 days, thirteen, or 76 per cent, showed either moderate or marked enlargement of the ovaries, while of the thirteen that survived this procedure for less than 30 days, only three, or 23 per cent, showed enlarged ovaries. These (Nos. 8, 12, and 13) survived suprarenalectomy 17, 24, and 27 days respectively, and represent, we believe, the lower limits as regards time in which obvious ovarian enlargement can take place in the presence of high grade suprarenal insufficiency. This enlargement consists essentially of an hypertrophy of the interstitial cells.

Of the rabbits in which the effects of partial suprarenalectomy were studied, twelve of the thirteen presented normal sized ovaries.

While the degree and frequency of ovarian hypertrophy following double suprarenalectomy cannot be brought into mathematical relation

with the duration of life after double suprarenalectomy, still there is a striking general relation.

Nineteen additional experiments in which double or partial suprarenalectomy was complicated by pregnancy were not included because it is well known that hypertrophy of the interstitial cells occurs during pregnancy. Lane-Claypon, studying a large number of rabbits, gives 17 micra as the average diameter of the interstitial cells of normal adult ovaries. During pregnancy these cells enlarge and reach a maximum of 32 micra on the 22nd day. Shortly after pregnancy the ovary undergoes regression, reaching its former size within 2 months. The ovarian enlargement observed in the present study following double suprarenalectomy could not be attributed to previous pregnancies as many of the animals were known never to have been pregnant, and, in addition, the list of partially suprarenalectomized rabbits includes a number of animals that were pregnant several times but in which the ovaries were of normal size at autopsy. This confirms the work of others with regard to regression of the ovary following pregnancy. Functional enlargement of the ovaries also occurs in other associations than pregnancy and suprarenal injury. It has been shown that compensatory hypertrophy follows partial castration (30), and that the hypertrophy is approximately proportional to the amount of ovarian tissue removed. There is also evidence that the interstitial cells of the ovary enlarge with the suprarenal cortex in chronic infections in rabbits.

As to the fate of the interstitial cells, Kingsbury (18) confirms the conclusions of Saimont and others that they are transient structures. He worked on cats. He further agrees with Saimont that their fate is not one of degeneration but that they revert back to the cell type from which they developed, which he believes is the stroma cell. However, the belief that they may develop from and revert back to a type morphologically resembling stroma cells is sufficient evidence that they are highly specialized cells.

The work reported here offers additional physiological evidence for the interrelation that has been suspected for some time from clinical observation. Most of the previous experimental work attempting to clarify the problem of suprarenal-gonadal interrelation has dealt with the effects of pregnancy, castration, and ovulation on the suprarenal cortex. The mechanism of the production of ovarian hypertrophy

following double suprarenalectomy is not understood. A plausible interpretation is that the enlargement is compensatory and in support of this are the facts that removal of the gonads, pregnancy, and ovulation also induce an hypertrophy of the suprarenal cortex. These facts clearly indicate an apparent reciprocal relation between these tissues.

CONCLUSIONS.

1. Moderate or marked ovarian enlargement has been observed in 76 per cent of rabbits which survived double suprarenalectomy over 30 days.

2. The ovarian enlargement consists essentially of an hypertrophy of the interstitial cells.

3. The hypertrophy of the interstitial cells is a compensatory reaction and adds further data to the functional interrelation between the suprarenal cortex and the interstitial cells.

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