STUDIES ON THE MECHANISM OF NIDATION

XXII. EFFECT OF HYPOPHYSECTOMY ON INDUCTION OF DECIDUALIZATION AND ON ITS REGRESSION*

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Summary. Successful induction of decidualization on the 4th day of pseudopregnancy (L_4) is possible in rats hypophysectomized on L_3 of pseudopregnancy (after 19.00 hours). However, in the absence of exogenous hormone, the decidual cell reaction cannot be maintained in the hypophysectomized rat. The effect of hypophysectomy on decidualization which is already established depends upon the time of removal of the pituitary. When hypophysectomy was performed before the 11th day of pseudopregnancy (L_{11}) breakdown and resorption of the deciduomata occurred within 4 days; when hypophysectomy was carried out on L_{11} or L_{12} , the deciduomata were resorbed more slowly. This relatively prolonged resorption was related to the absence of ovulation at the end of the period of pseudopregnancy in the hypophysectomized rats. The results indicate that no luteotrophic factor of uterine or decidual origin is produced in the pseudopregnant rat bearing deciduomata.

INTRODUCTION

Decidualization is a prerequisite for successful nidation (Shelesnyak, 1957). It has been claimed that the hormonal requirements of experimentally produced decidualization are similar to those of nidation and associated decidualization (Shelesnyak, 1960). Recently, Varavudhi, Lobel & Shelesnyak (1966) have shown that nidation took place at the normal time, on L_5 , in pregnant rats which were hypophysectomized on L_3 (after 19.00 hours) in the absence of the administration of hormone. However, nidation did not occur if ovariectomy was performed together with the hypophysectomy. Similarly, decidualization could not be induced on L_4 in pseudopregnant rats ovariectomized on the same day (Lobel, Tic & Shelesnyak, 1965). If the hormonal requirements for nidation and experimental induction of decidualization are indeed similar, then it should be possible to induce decidualization in pseudopregnant rats hypophysectomized only on the evening of L_3 or the morning of L_4 .

The question whether decidual tissue free of any contaminating foetal

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elements contains a luteotrophic factor has not yet been decided. It has been suggested that the maintenance of decidual tissue and the corpora lutea are directly related to each other (Burrows, 1949). Averill, Ray & Lyons (1950) thought that decidual tissue might somehow be concerned with a secretory process in the ovary, because extracts of maternal placenta (i.e. decidual tissue) were occasionally able to maintain gestation in L_6 hypophysectomized pregnant rats. Nalbandov (1961) and Semmelwitz, Aldred & Nalbandov (1961) put forward the hypothesis that a factor of uterine origin maintains the life of corpora lutea of both pregnant and pseudopregnant rats. But, so far, no investigations have been reported on the effect of decidualization (experimentally produced) on corpora lutea in hypophysectomized animals and thus to find out whether such corpora lutea are able to maintain the deciduomata.

In addition, it has been shown (Lobel *et al.*, 1965) that the occurrence of the first ovulation terminating the period of pseudopregnancy in rats bearing deciduomata affects the regression of the decidual tissue. Therefore a study was undertaken to determine the effect of hypophysectomy on the maintenance and termination of decidualization, when the removal of the gland was performed at different times after decidualization had been established. This report is divided into two parts: the first deals with the induction of decidualization in hypophysectomized rats, the second with the effect of hypophysectomy on decidualization after its induction.

MATERIALS AND METHODS

The rats used were adult, virgin, female rats of the Biodynamics colony, originating from Wistar stock. The animals were kept in an air-conditioned environment, with a natural light cycle and Purina laboratory chow and tap water were available *ad libitum*. Body weights and vaginal smears were recorded daily, both before and throughout the course of the experiments. Only animals having regular 4 or 5 day oestrous cycles were used. In this laboratory, the day on which a vaginal plug is found or spermatozoa are observed in the vaginal smear, is designated as L_0 and subsequent days as $L_1, L_2, \dots L_n$. The L denotes a leucocytic type of vaginal smear. In pseudopregnancy, L_1 denotes the day after cervical stimulation and L_2, L_3 , etc., the days following. This convention permits the synchronous timing of phenomena which occur both in early pregnancy and in pseudopregnancy.

Pseudopregnancy was induced in 104 rats by faradic stimulation of the cervix uteri at pro-oestrus and oestrus (Shelesnyak, 1931). On the day following the second electrical stimulation, the vaginal smear became leucocytic, this day was designated as L_1 of pseudopregnancy. The pseudopregnant animals were then divided into two groups and treated as follows:

Group I consisted of twenty-five pseudopregnant rats. Seventeen were hypophysectomized at different times from 09.00 hours on L_3 to 12.00 hours on L_4 (Table 1). Eight were sham-operated. Decidualization was induced in both hypophysectomized and sham-operated control rats by the intraluminal instillation of histamine acid phosphate, 1 μ g in 0.1 ml of de-ionized and distilled water into each uterine horn at 10.00 hours on L_4 , the time of maximal

uterine sensitivity (Shelesnyak & Kraicer, 1961a). The animals were autopsied on L₅, L₆ and L₇ (see Table 1). The 'physiological' method for induction of decidualization (Shelesnyak & Kraicer, 1961b) was not used in this study because of the great sensitivity of hypophysectomized animals to the systemic release of histamine (Perla, 1935; Marcus, Kraicer & Shelesnyak, 1963).

TABLE 1

INDUCTION OF DECIDUALIZATION IN HYPOPHYSECTOMIZED PSEUDOPREGNANT RATS

Time of hypophysectomy	Day of autopsy	Animals with DCR*/group	Wet weight (mg/100 g body weight) ($M \pm SEM$)		
			Uterus	Ovaries	Adrenals
L ₃ , 09.00 to 12.00 hours	L ₇	0/4	127.7 $\pm$ 12.6	25.9 $\pm$ 1.1	20.8 $\pm$ 2.5
L ₃ , 19.00 to 22.00 hours	L ₇	4/5	187.4 $\pm$ 15.6	28.1 $\pm$ 2.0	27.3 $\pm$ 1.6
L ₄ , 09.00 to 12.00 hours	L ₅	2/2	310.9 $\pm$ 4.0	38.2 $\pm$ 1.2	47.0 $\pm$ 1.1
L ₄ , 09.00 to 12.00 hours	L ₆	2/2	247.7 $\pm$ 49.5	32.4 $\pm$ 2.1	29.9 $\pm$ 3.1
L ₄ , 09.00 to 12.00 hours	L ₇	3/4	237.7 $\pm$ 41.9	26.2 $\pm$ 1.0	24.1 $\pm$ 2.4
Sham-operated control L ₃ , 09.00 to 12.00 hours	L ₇	8/8	905.2 $\pm$ 120.4	30.0 $\pm$ 0.8	

* Decidualization induced on L₄.

Hypophysectomized animals which received an intraluminal injection of histamine acid phosphate showed no signs of histamine shock.

Group II consisted of ninety-three pseudopregnant rats: forty-five were experimental animals and forty-eight were sham-operated. Hypophysectomies and sham-operations were performed at different times between L₅ and L₁₁.

TABLE 2

EFFECT OF HYPOPHYSECTOMY ON DECIDUALIZATION

Day of hypophysectomy or sham-operation	Day of autopsy	Animals with DCR*/group		Wet weight (mg/100 g body weight) ($M \pm SEM$)			
				Uterus		Ovaries	
		Hypo-physectomy	Sham-operation	Hypo-physectomy	Sham-operation	Hypo-physectomy	Sham-operation
L ₅	L ₉	0/5	4/4	145.7 $\pm$ 22.6	1518.9 $\pm$ 347.3	23.2 $\pm$ 3.5	24.7 $\pm$ 1.9
L ₇	L ₁₁	0/5	6/6	223.2 $\pm$ 24.4	1714.1 $\pm$ 377.2	24.5 $\pm$ 1.5	29.0 $\pm$ 2.0
L ₉	L ₁₃	0/5	4/5	235.5 $\pm$ 16.8	1420.8 $\pm$ 330.6	28.7 $\pm$ 2.4	29.7 $\pm$ 2.4
L ₁₀	L ₁₄	0/6	5/6	335.1 $\pm$ 32.5	1575.0 $\pm$ 313.2	25.4 $\pm$ 1.7	26.1 $\pm$ 0.8
L ₁₁	L ₁₃	3/3	4/5	1529.7 $\pm$ 280.3	1420.8 $\pm$ 330.6	38.5 $\pm$ 4.6	29.7 $\pm$ 2.4
L ₁₁	L ₁₅	7/10	6/9	746.1 $\pm$ 155.4	974.5 $\pm$ 270.8	24.9 $\pm$ 0.8	32.8 $\pm$ 2.4
L ₁₁	L ₁₇	3/6	3/6	533.1 $\pm$ 128.0	934.3 $\pm$ 357.9	26.4 $\pm$ 1.8	34.0 $\pm$ 2.0
L ₁₂	L ₁₆	4/5	5/7	376.0 $\pm$ 84.0	966.4 $\pm$ 199.8	26.2 $\pm$ 2.5	26.9 $\pm$ 1.7

* Decidualization induced on L₄.

as shown in Table 2. With the exception of rats hypophysectomized or sham-operated on L₅ all animals were laparotomized on L₇; the uteri were exposed and decidual induction was scored according to the method of Shelesnyak & Kraicer (1961b). Only animals whose uteri exhibited a decidual score of 3 or

4 for each uterine horn were used for the study. It was established before the start of the experiments that uteri, which showed a score of 3 or 4 at laparotomy on L₇, subsequently exhibited a maximal degree of decidual development. The rats were killed 2, 4 or 6 days after hypophysectomies or sham-operations (Table 2). Details concerning the methods of hypophysectomy, ovariectomy and laparotomy have been described previously (Varavudhi, 1965).

Evaluation of results

The following parameters were used: (1) wet weights of the uteri, ovaries and adrenals; (2) configuration of the vaginal smear; and (3) histological picture of the uteri and ovaries.

The mean and standard errors of the mean of the organ weights were determined on the basis of 100 g body weight.

RESULTS

Induction of decidualization in hypophysectomized pseudopregnant rats

The results are summarized in Table 1, and shown in Pl. 1, Figs. 1 and 2. Decidualization was induced on L₄ in hypophysectomized pseudopregnant rats, when hypophysectomy was performed as early as 19.00 hours on the previous day (L₃). Following induction on L₄ in the hypophysectomized rats, the decidual cell reaction developed on the antimesometrial side of the lumen in the form of nodular swellings (Pl. 1, Fig. 1). The development of the decidual cell reaction was reflected in the increased uterine wet weight (see Table 1). On L₅ many mitoses were observed in the endometrial cells in the regions of the nodules (Pl. 1, Fig. 2). Subsequent cell growth and multiplication could not be maintained in the absence of the pituitary; the number of mitoses declined rapidly and the uteri showed no further increase in weight. Thus, the

EXPLANATION OF PLATE 1

FIGS. 1 and 2. Decidualization in hypophysectomized pseudopregnant rats. Hypophysectomy L₃, induction of decidualization L₄, autopsy L₅. Sections of uterus stained with haematoxylin and eosin. Fig. 1, $\times$ about 75. Transverse section. Nodular decidual cell reaction on anti-mesometrial side of the lumen; n.d. nodule of decidualizing endometrium. Fig. 2, $\times$ about 300. Note mitoses in the endometrium; some are indicated by arrows. l, Lumen; e, epithelium.

FIG. 3. Development of metrial gland. Pseudopregnant rat sham-operated on L₁₁, autopsy L₁₃. Section of the uterus stained with haematoxylin and eosin; $\times$ about 300. Mesometrial area showing mitoses (m) in vicinity of blood vessels (bv).

FIG. 4. Metrial gland. Pseudopregnant rat sham-operated L₁₂, autopsy L₁₆. Section of uterus stained with haematoxylin and eosin; $\times$ about 30. Numerous large metrial gland cells in mesometrial area.

FIG. 5. Mesometrial area in hypophysectomized pseudopregnant rat. Hypophysectomy L₁₁, autopsy L₁₃. Section of uterus stained with haematoxylin and eosin; $\times$ about 75. Comparatively few metrial gland cells (mg) are seen in vicinity of the blood vessels (bv).

FIG. 6. Control rat sham-operated L₁₁, autopsy L₁₅. Section of uterus stained with haematoxylin and eosin; $\times$ about 30. No decidual tissue left in uterus and reorganization of endometrium (e) nearly completed.

FIG. 7. Delayed resorption of deciduomata. Pseudopregnant rat hypophysectomized on L₁₁, autopsy L₁₅. Section of uterus stained with haematoxylin and eosin; $\times$ about 30. Deciduoma (d) still present in uterus; m, myometrium.

PLATE 1

(Facing p. 352)

PLATE 2

decidual reaction, which had been successfully induced, declined from L₆ onwards. This regression was accompanied by some haemorrhage into the lumen, and between L₆ and L₇ blood was observed in the vaginal smears. At autopsy, the endometria were soft and haemorrhagic and the uterine wet weights of the hypophysectomized animals were significantly lower than those of the sham-operated controls (see Table 1). At the same time, the deciduomata in the uteri of the sham-operated control animals (with intact pituitaries) were well developed and showed many mitoses, and the uterine wet weights were high.

Effect of hypophysectomy after induction of decidualization

The results are summarized in Table 2 and shown in Pl. 1, Figs. 3 to 7, and Pl. 2, Figs. 8 to 10. When hypophysectomy was performed before L₁₁ (from L₅ to L₁₀) blood appeared in the vaginal smear within 24 hr of the removal of the pituitaries. This external haemorrhage was interpreted as a sign of the breakdown of decidual tissue. The vaginal bleeding persisted for a few days, but in most cases had ceased before autopsy 4 days after hypophysectomy. Rats hypophysectomized on L₅ showed less vaginal bleeding than those hypophysectomized on later dates. At autopsy, 4 days after hypophysectomy, the uterine wet weights were considerably lower than those of the sham-operated controls (see Table 2), and the deciduomata had regressed. When hypophysectomy was performed on L₁₁ and L₁₂ vaginal bleeding occurred within 24 hr of operation and continued until autopsy 2, 4 and 6 days later. At autopsy, decidual tissue was still present within the uteri and the area of the mesometrial triangle was only moderately enlarged due to the presence of the metrial gland (Pl. 1, Figs. 5 and 7). Mitoses were rarely observed in this region in the hypophysectomized animals and the lack of mitotic activity undoubtedly contributed to the poor development of the metrial gland. Resorption of the deciduomata did not proceed as rapidly after hypophysectomy on L₁₁ and L₁₂, as when hypophysectomy was performed on earlier days.

The vaginal smears of all hypophysectomized animals retained a dioestrous leucocytic pattern indicating absence of follicular activity due to ablation of the pituitary.

In the control animals, a transitory vaginal bleeding occurred in most cases after the sham-operation. Animals sham-operated from L₅ to L₁₀ had large deciduomata in the uteri at autopsy 4 days later. Animals not autopsied before L₁₂, showed a second vaginal bleeding at this time associated with the regression of the deciduomata at the normal time. Animals sham-operated on L₁₁ and

EXPLANATION OF PLATE 2

FIG. 8. Follicular development at termination of pseudopregnancy. Pseudopregnant rat sham-operated on L₁₁, autopsy L₁₃. Section of ovary stained with haematoxylin and eosin; $\times$ about 30. Note large vesicular follicles (f) and beginning involution of corpus luteum (cl).

FIG. 9. Regression of follicles in hypophysectomized rat. Pseudopregnant rat hypophysectomized on L₁₁, autopsy L₁₃. Section of ovary stained with haematoxylin and eosin; $\times$ about 30. Note regression of follicles, and large and well preserved luteal cells.

FIG. 10. Cords of luteal cells from corpus luteum shown in Fig. 9. $\times$ about 75.

L₁₂ had vaginal bleeding on the days following, presumably due to both the sham-operation and the regression of the deciduomata at the normal time. From L₁₂ to L₁₆ the control uteri showed many mitoses in the vicinity of the blood vessels in the mesometrial area (Pl. 1, Fig. 3) as the metrial gland developed. A large metrial gland developed in all cases; this probably contributed to the comparatively high uterine wet weights, since the decidual tissue in these uteri had regressed to a considerable extent (Pl. 1, Fig. 6).

All animals in the sham-operated control groups showed a pro-oestrous type vaginal smear by L₁₇ revealing that follicular development had occurred.

The ovarian weights of the hypophysectomized animals were not much below those of sham-operated controls (Table 2) confirming the report of Liu & Noble (1939) that the ovary does not change much in wet weight during the first days after hypophysectomy. Histological sections of the ovaries of sham-operated animals (from L₁₂ onwards) revealed the presence of large vesicular follicles which were not seen in the ovaries of hypophysectomized animals (Pl. 2, Figs. 8 and 9). These follicles undoubtedly contributed to the weight of the ovaries of the sham-operated control groups, especially towards the stage of termination of the pseudopregnancy and the onset of ovulation. In addition, the ovaries of hypophysectomized rats contained corpora lutea which appeared well-preserved, while the corpora in the ovaries of the sham-operated animals exhibited signs of involution and shrinkage (Pl. 2, Figs. 8 to 10).

DISCUSSION

Induction of decidualization in hypophysectomized rats

The results show that decidualization may be induced in hypophysectomized rats. Astwood & Greep (1938) reported that it is not possible to induce decidualization in hypophysectomized pseudopregnant rats. The basis for our success in producing decidualization and their failure may be temporal. An interesting question which arises is that of the survival and function of corpora lutea after hypophysectomy.

Smith (1930) showed that corpora lutea remained in the ovary of the rat as long as 15 months after hypophysectomy; Levy, Deane & Rubin (1959) demonstrated the presence of an enzyme involved in steroidogenesis (3 β -hydroxysteroid dehydrogenase) in corpora lutea of rats 1½ months after hypophysectomy. Obviously, the corpora lutea observed after hypophysectomy are the last set produced before the excision of the pituitary. Therefore, in the absence of the pituitary and consequently of a stimulus to form a new crop of developing follicles, the normal 'life cycle' of the existing set of corpora lutea is arrested. Moreover, involution does not occur within a matter of days as during the normal oestrous cycle. Survival of corpora lutea, however, is not synonymous with functional activity; and the presence of the specific enzyme does not imply that hormones are being synthesized and/or released. This study shows that the ovary (presumably containing corpora lutea) does continue to function for a short period of time following hypophysectomy because not only is decidualization initiated, but also some decidual growth takes place. This can only occur in the presence of progesterone. However, by L₇, 4 days after

pituitary ablation, the amount of progesterone available is insufficient for maintaining decidual growth and the decidual tissue degenerates with haemorrhage. Vaginal smears reflect this degeneration and blood appears in the smear.

Effect of hypophysectomy after induction of decidualization

Following induction of decidualization on L₄ in intact pseudopregnant rats, uterine growth and weight increase rapidly, so that by L₈ an eight- to ten-fold increase has occurred and the values reach 2000 to 3000 mg. However, when hypophysectomy was performed between L₅ and L₁₀, the process of decidualization was promptly halted; the deciduomata regressed and, at autopsy 4 days later, the uterine weights had decreased. This was seen even in the case of animals hypophysectomized on L₉ and L₁₀, i.e. after the major increase in uterine weight had occurred. These results indicate that no luteotrophic factor is produced by the decidual tissue itself. Under these experimental conditions, deciduomata apparently do not directly affect the ovary as suggested by Nalbandov (1961) and Semmelwitz, Aldred & Nalbandov (1961), because in the absence of the pituitary, the ovary could not maintain the deciduomata.

When the effect of hypophysectomy after L₁₀ is analysed, the actual life span of deciduomata must be taken into consideration. Decidual tissue under optimal conditions for maintenance has a limited life span; this appears to be an intrinsic characteristic of the tissue (Shelesnyak, 1962). Furthermore, within the limits imposed by its own life span, decidual tissue may be adversely affected by alterations in its hormonal environment (for references, see Tic, 1965) in this case, by the hypophysectomy.

Deciduomata appear to be particularly sensitive in this respect during the initiation and the growth period, as witnessed by the prompt appearance of vaginal bleeding and termination of decidualization when hypophysectomy was performed during this growth period. A different situation is encountered, however, when hypophysectomy is performed on L₁₁ and L₁₂. At this time, deciduomata have completed their growth and normal resorption has begun. Concurrently, the metrial gland develops and it is most probably this development which maintains a high uterine weight in spite of the regression of the decidual tissue. In intact animals, regression of deciduomata is associated with the development of a large metrial gland. Though its function is unknown, the possibility exists that the metrial gland is in some way concerned with the resorption of decidual tissue. If this is correct, then the poor development of the metrial gland in the hypophysectomized animals would contribute to the delay in resorption.

The LH and FSH potency of the adenohypophysis has been found highest between L₉ and L₁₁ of pseudopregnancy (Rothchild, 1962; Schwarz & Rothchild, 1964). Furthermore, Eto, Masuda, Shzuki & Hosi (1962) and Armstrong, O'Brien & Greep (1964) have demonstrated that administration of LH caused immediate release of progesterone from luteinized rat ovaries both *in vivo* and *in vitro*. Finally it has been shown that ovulation occurs around L₁₂ in some pseudopregnant rats which are bearing deciduomata (Lobel *et al.*, 1965). Therefore, this period (L₁₁ and L₁₂) appears to be a critical one during pseudopregnancy from the point of view of the pituitary, the ovary and the uterus.

It is, in fact, the beginning of the termination of pseudopregnancy (Shelesnyak, 1931) in the rat which does not bear any deciduomata. When hypophysectomy is performed on L₁₁ and L₁₂, it is possible that the release of LH has already occurred, thus the existing corpora lutea are stimulated to secrete progesterone, whilst, because of the hypophysectomy, the follicles cannot grow and mature. Since ovulation is associated with an accelerated rate of absorption of deciduomata, it is reasonable to suppose that the lack of ovulation will be associated with a slowing down in regression of the decidual tissue. This is what is observed in the experimental results. The uterine weights at autopsy of animals hypophysectomized on L₁₁ and L₁₂ are high when compared with those of animals hypophysectomized at earlier stages (L₉ and L₁₀). This must, in part, be due to a delayed resorption of the decidual tissue since such tissue was still present in the uteri, and the metrial glands of these uteri were considerably smaller than the metrial glands of the sham-operated controls.

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REFERENCES

- ARMSTRONG, D. T., O'BRIEN, J. & GREEP, R. O. (1964) Effects of luteinizing hormone on progesterin bio-synthesis in the luteinized rat ovary. *Endocrinology*, **75**, 488.
- ASTWOOD, E. B. & GREEP, R. O. (1938) A corpus luteum stimulating substance in rat placenta. *Proc. Soc. exp. Biol. Med.* **38**, 713.
- AVERILL, S. C., RAY, E. B. & LYONS, W. R. (1950) Maintenance of pregnancy in hypophysectomized rats with placental implants. *Proc. Soc. exp. Biol. Med.* **75**, 3.
- BURROWS, H. (1949) *Biological action of sex hormones*, 2nd edn. Cambridge University Press.
- ETO, T., MASUDA, H., SHZUKI, Y. & HOSI, T. (1962) Progesterone and pregn-4-ene-20 α (-ol-3-one) in rat ovarian venous blood at different stages in reproductive cycle. *Jap. J. Anim. Reprod.* **8**, 34.
- LEVY, H., DEANE, H. W. & RUBIN, B. L. (1959) Visualisation of steroid 3 β -ol-dehydrogenase activity in tissues of intact and hypophysectomized rats. *Endocrinology*, **65**, 937.
- LIU, S. H. & NOBLE, R. L. (1939) The effect of extracts of serum and human pregnancy urine on the reproductive systems of hypophysectomized female rats. *J. Endocr.* **1**, 15.
- LOBEL, B. L., TIC, L. & SHELESNYAK, M. C. (1965) Histochemical analysis of decidualization in the rat. *Acta endocr., Copenh.* **50**, 452.
- MARCUS, G. J., KRAICER, P. F. & SHELESNYAK, M. C. (1963) Studies on the mechanism of decidualization. II. Histamine releasing action of pyrathiazine. *J. Reprod. Fert.* **5**, 409.
- NALBANDOV, A. V. (1961) Comparative physiology and endocrinology of domestic animals. *Recent Prog. Horm. Res.* **17**, 119.
- PERLA, D. (1935) Effect of anterior hypophysial emulsion on natural resistance of hypophysectomized and normal rats to histamine poisoning. *Proc. Soc. exp. Biol. Med.* **35**, 121.
- ROTHCHILD, I. (1962) Corpus luteum-pituitary relationship: The effect of progesterone on folliculotrophic potency in the rat. *Endocrinology*, **70**, 303.
- SCHWARTZ, N. B. & ROTHCHILD, I. (1964) Changes in pituitary LH concentration during pseudopregnancy in the rat. *Proc. Soc. exp. Biol. Med.* **116**, 107.
- SEMMELWITZ, P. H., ALDRED, J. P. & NALBANDOV, A. V. (1961). Mechanisms of maintenance of corpora lutea in pigs and rats. *J. Reprod. Fert.* **2**, 378.
- SHELESNYAK, M. C. (1931) The induction of pseudopregnancy in the rat by means of electrical stimulation. *Anat. Rec.* **49**, 179.
- SHELESNYAK, M. C. (1957) Some experimental studies on the mechanism of ova implantation in the rat. *Recent Prog. Horm. Res.* **13**, 2, 69.
- SHELESNYAK, M. C. (1960) Nidation of fertilized ovum. *Endeavour*, **19**, 81.
- SHELESNYAK, M. C. (1962) Decidualization: The decidua and the deciduoma. *Perspect. Biol. Med.* **5**, 503.

- SHELESNYAK, M. C. & KRAICER, P. F. (1961a) Time limits of uterine sensitivity during progestation. *Acta endocr., Copenh.* Suppl. 51, p. 547.
- SHELESNYAK, M. C. & KRAICER, P. F. (1961b) A physiological method for inducing decidualization of the rat uterus: Standardization and evaluation. *J. Reprod. Fert.* 2, 438.
- SMITH, P. E. (1930) Hypophysectomy and replacement therapy in the rat. *Am. J. Anat.* 45, 205.
- TIG, L. (1965) *Growth pattern of the decidualizing rat uterus: Estimation of protein and nucleic acids*. Ph.D. thesis, Hebrew University, Jerusalem.
- VARAVUDHI, P. (1965) *Studies on the mechanism of nidation and the interrelationships between the central nervous system, the adenohypophysis and the ovary*. Ph.D. thesis, Rehovoth, Israel.
- VARAVUDHI, P., LOBEL, B. L. & SHELESNYAK, M. C. (1966) Effects of hypophysectomy and ovariectomy on nidation in pregnant rats. (In press).