THE EFFECT OF GONADOTROPHINS
AND OF GROWTH HORMONE ON THE DEVELOPMENT
OF OVARIAN AUTOGRRAFTS ON THE GREATER
OMENTUM OF HEMICASTRATED RATS

By
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ABSTRACT
Hemicastrated rats, 3, 8 and 16 weeks old with an ovarian autograft on
the greater omentum near the stomach, were injected daily during 1
month with follicle-stimulating hormone (NIH-FSH-S1 1 mg), luteinizing
hormone (NIH-LH-S1 1 mg or NIH-LH-S3 1.25 mg), prolactin (NIH-P-
S3 1 mg), growth hormone (NIH-GH-B2 6 mg or NIH-GH-B3 9 mg),
human chorionic gonadotrophin (HCG, Pregnyl® Organon 20 or 50 IU)
or pregnant mare's serum gonadotrophin (PMSG, Gestyl® Organon 20
or 50 IU) respectively. The mean weights of the implants in every group
were compared with those in control hemicastrated and castrated animals
of corresponding ages injected with saline or untreated.
In 8 week old rats GH, LH and P had no effect on the growth of the im-
plant, while FSH caused a considerable development of the graft. In
rats 3 week old HCG (20 IU daily) induced a slight increase in the weight
of the implants, while PMSG in the same dose was much more active. Im-
plants in animals 16 week old did not respond to injections of either
HCG or PMSG in doses of 20 IU daily. A higher dose (50 IU daily) of
PMSG, however, induced a very slight but significant development of the
ovarian grafts while HCG was still ineffective. The results obtained show
that ovarian autografts respond better to gonadotrophin stimulation in
younger than in older rats.
The mean weights of the implants that grew under the influence of FSH
or PMSG were statistically higher than in the control hemicastrated ani-
mals of corresponding age but smaller than in the castrated control rats.
Comparisons of the effect of the various hormones on the development of

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the ovarian implants and of the ovaries in situ led us to suggest that the ovary produces a substance which is not an oestrogen and which inhibits gonadotrophin action at the level of the ovarian graft.

In castrated rats, oestrogens produced by ovarian implants in organs draining into the portal circulation of the liver are inactivated before reaching the systemic blood supply. The lack of oestrogens stimulates the pituitary to produce larger amounts of gonadotrophins. It is assumed that the prolonged action of gonadotrophins, especially of FSH (Gardner 1948; Li & Gardner 1949), secreted by the uninhibited pituitary, stimulates the growth of the implant leading finally to the development of granulosa cell tumours (Biskind et al. 1953). In contrast, implants in hemicastrated rats and mice do not develop and remain »dormant« for many months (Ber 1970a; Biskind et al. 1950). After removal of the second ovary such implants start to grow immediately as in animals castrated bilaterally at the time of implantation (Ber 1970a).

In a small number of experiments performed in an attempt to stimulate the development of »dormant« implants by gonadotrophins no effect was found (Biskind et al. 1953; Wenner & Hofmann 1950). These observations were made exclusively on spleen-ovaries and the results have been based on visual inspection which does not allow an accurate measurement of the early development of the implant.

The method of implantation of a fragment of the ovary on the greater omentum near the stomach devised by us (Ber 1968a), however, allows an estimation of the weight of the implant and of its growth even in the very early stages. We, therefore, considered this method suitable for the examination of the effect of various gonadotrophins on the development of »dormant« implants.

In addition to gonadotrophins we investigated the effect of pituitary growth hormone since experiments carried out previously by other investigators suggested that it enhances the growth of ovaries in hypophysectomized rats (Moon et al. 1951), prevents the atrophy of spleen-ovaries in hypophysectomized rats (Fels et al. 1965) and promotes the development of tumours in rat ovaries in situ (Evans et al. 1948; Moon et al. 1950).

MATERIALS AND METHODS

The experiments were carried out on albino rats belonging to the same stock, inbred to some extent, but without special brother-sister mating. They received purina chow food and water ad libitum.

The effect of pure hormones was investigated on 8 week old animals (body weight 115 g ± 10%0). Rats of this age have been generally used by us, but since ovarian implants develop much better the younger the animals (Ber 1968b, 1970b), experiments designed to investigate the influence of human chorionic gonadotrophin and pregnant

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mare's serum gonadotrophin were performed on rats aged 3 weeks (b.w. 30 g ± 10\%o) and 16 weeks (b.w. 180 g ± 10\%o) respectively.

All the animals were hemicastrated under ether anaesthesia. At the same time an implantation of a fragment of the removed ovary was made on the greater omentum near the stomach, according to a technique described previously (Ber 1968a). Some of the operated animals served as controls and in order to evaluate a possible deleterious effect of the daily handling of the rats, some of the control animals were injected with 0.5 ml saline daily. The remaining rats received daily subcutaneous injections of 0.5 solutions of the investigated hormones in saline, starting on the day after operation.

The following hormones have been used: Follicle-stimulating hormone (NIH-FSH-S1 1 mg/day), luteinising hormone (NIH-LH-S1 1 mg/day and NIH-LH-S3 1.25 mg/day, corresponding to 1 mg/day of NIH-LH-S1), prolactin (NIH-P-S3 1 mg/day), growth hormone (NIH-GH-B2 6 mg/day and NIH-GH-B3 9 mg/day, almost equivalent to 6 mg/day of NIH-GH-B2), human chorionic gonadotrophin (HCG, Pregnyl® Organon) and pregnant mare’s serum gonadotrophin (PMSG, Gestyl® Organon) 20 or 50 IU daily.

Ovarian implantations were also performed in a number of bilaterally castrated rats of the same age groups as the hemicastrated rats. Some of them received daily injections of 0.5 ml saline subcutaneously, while the other rats were not treated.

All the animals were killed one month after operation. Weighing of the implants and of the ovaries and histological examinations were carried out as described previously (Ber 1968a). The results obtained were analysed statistically using Student's t test of significance. A probability of $P < 0.05$, was considered as statistically significant.

**RESULTS**

In all the hemicastrated control animals the grafts took well but failed to grow. The mean weight of the implants in animals treated with saline (Fig. 1D) did not differ from that of the untreated ones (Fig. 1C). The histological pictures of the implants in the control animals were similar, showing primary follicles, very small Graafian follicles and single very small corpora lutea. Therefore, the data from both injected and untreated control rats were taken together, and the mean weights of the implants in the animals belonging to the three age groups were found to be 3.1, 5.0 and 3.0 mg respectively (Table 1A).

In the bilaterally castrated animals the development of the implants was more marked in the younger animals, in agreement with previous observations (Ber 1968b). No differences were found in the degree of development of implants in animals of the same age between those injected with saline (Fig. 1B) and untreated ones (Fig. 1A) and, hence, the data for each age group were combined. The mean weights of the implants in the 3, 8 and 16 weeks old animals were 122.0, 31.3 and 22.7 mg respectively (Table 1H). The histological

* The pure hormones were kindly supplied by the Endocrinology Study Section, National Institutes of Health, Bethesda, U.S.A.
Fig. 1.

Ovarian implants in control castrated and hemicastrated rats and in hemicastrated animals treated with various hormones.

A - castrated, B - castrated injected with saline, C - hemicastrated, D - hemicastrated injected with saline, E - hemicastrated injected with NIH-GH, F - hemicastrated injected with NIH-LH, G - hemicastrated injected with NIH-FSH, H - hemicastrated injected with NIH-P.

Pictures of the implants in castrated rats of the three age groups were similar to those described previously (Ber 1968b) consisting mostly of corpora lutea, small luteal cysts, mixed follicles and single primary and Graafian follicles.

In hemicastrated animals treated with FSH a visible development of the implants occurred (Table 1D and Fig. 1G), the mean weight being significantly higher than in control animals of the same age (Table 2).

In rats treated with PMSG (20 IU daily) a statistically significant development of the graft (Table 2) was noticed only in the younger age group (Table
Table 1.
Mean weight of ovaries and ovarian implants in hemicastrated rats treated with various hormonal preparations during 1 month.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of animals</th>
<th>Initial age in weeks</th>
<th>Substance injected</th>
<th>Mean weight of implants in mg ± se*</th>
<th>Mean weight of ovaries in mg ± se</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aa</td>
<td>20</td>
<td>3</td>
<td>-</td>
<td>3.1 ± 0.4</td>
<td>56.1 ± 3.5</td>
</tr>
<tr>
<td>Ab</td>
<td>46</td>
<td>8</td>
<td>NIH-GH</td>
<td>5.0 ± 0.6</td>
<td>60.3 ± 1.4</td>
</tr>
<tr>
<td>Ac</td>
<td>18</td>
<td>16</td>
<td>NIH-LH</td>
<td>3.0 ± 0.4</td>
<td>64.7 ± 3.3</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
<td>8</td>
<td>NIH-FSH</td>
<td>5.3 ± 1.1</td>
<td>69.4 ± 9.3</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>8</td>
<td>NIH-P</td>
<td>6.3 ± 2.1</td>
<td>123.6 ± 12.4</td>
</tr>
<tr>
<td>D</td>
<td>25</td>
<td>8</td>
<td>NIH-FSH</td>
<td>14.1 ± 2.6</td>
<td>124.1 ± 10.5</td>
</tr>
<tr>
<td>E</td>
<td>13</td>
<td>8</td>
<td>NIH-P</td>
<td>5.2 ± 0.7</td>
<td>73.5 ± 3.8</td>
</tr>
<tr>
<td>Fa</td>
<td>15</td>
<td>3</td>
<td>HCG(20)*</td>
<td>7.1 ± 0.9</td>
<td>79.6 ± 5.9</td>
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<tr>
<td>Fb</td>
<td>12</td>
<td>16</td>
<td>HCG(20)</td>
<td>1.9 ± 0.5</td>
<td>76.3 ± 8.4</td>
</tr>
<tr>
<td>Fc</td>
<td>12</td>
<td>16</td>
<td>HCG(50)</td>
<td>4.7 ± 1.6</td>
<td>95.8 ± 8.8</td>
</tr>
<tr>
<td>Ga</td>
<td>15</td>
<td>3</td>
<td>PMSG(20)</td>
<td>32.5 ± 4.1</td>
<td>243.9 ± 11.6</td>
</tr>
<tr>
<td>Gb</td>
<td>12</td>
<td>16</td>
<td>PMSG(20)</td>
<td>2.6 ± 0.9</td>
<td>95.2 ± 6.6</td>
</tr>
<tr>
<td>Gc</td>
<td>11</td>
<td>16</td>
<td>PMSG(50)</td>
<td>7.6 ± 1.5</td>
<td>187.9 ± 10.8</td>
</tr>
<tr>
<td>Ha</td>
<td>61</td>
<td>3</td>
<td>Bilaterally</td>
<td>122.0 ± 5.4</td>
<td>-</td>
</tr>
<tr>
<td>Hb</td>
<td>15</td>
<td>8</td>
<td>castrated</td>
<td>31.3 ± 4.5</td>
<td>-</td>
</tr>
<tr>
<td>Hc</td>
<td>36</td>
<td>16</td>
<td>untreated</td>
<td>22.7 ± 2.3</td>
<td>-</td>
</tr>
</tbody>
</table>

* Standard error of the mean.
** In brackets the doses injected daily in IU.

1 Ga) while in the older group no effect was observed (Table 1 Gb and Table 2). However, with 50 IU PMSG daily a slight but significant increase in the mean weight of the implant in the oldest animals occurred (Table 1 Gc and Table 2).

In none of the groups treated with FSH or PMSG did the mean weight of the implant reach the level found in bilaterally castrated animals of corresponding age (Table 1H), the differences between them being highly significant (Table 2).

In rats treated with LH a slight stimulation of the growth of the implant was observed (Table 1C and Fig. 1F) which was, however, not statistically significant (Table 2). In animals injected with GH and P the grafts did not differ from those in the control animals (Fig. 1E, H, Table 1B, E and Table 2).

In the youngest age group treated with HCG (Table 1 Fa) a significant, although slight difference in comparison to the control animals, was observed.
Table 2.
Statistical analysis of the differences of the mean weights of implants between experimental and control rats.

<table>
<thead>
<tr>
<th>Groups* compared</th>
<th>Aa</th>
<th>Av</th>
<th>Ac</th>
<th>Ha</th>
<th>Hb</th>
<th>Hc</th>
</tr>
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<tbody>
<tr>
<td>B</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
<td>t = 5.7</td>
<td>Ø</td>
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</tr>
<tr>
<td></td>
<td>*p &gt; 0.8</td>
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<td></td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
<td>t = 5.1</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td></td>
<td>*p &gt; 0.5</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Ø</td>
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<td>t = 3.3</td>
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<td>E</td>
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</tr>
<tr>
<td></td>
<td>*p &gt; 0.9</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
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</tr>
<tr>
<td>Fa</td>
<td>t = 4.06</td>
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<td>Ø</td>
<td>t = 21.0</td>
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<td>Ø</td>
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<tr>
<td></td>
<td>*p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Fb</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
<td>t = 1.7</td>
<td>Ø</td>
<td>Ø</td>
</tr>
<tr>
<td></td>
<td>*p &gt; 0.05</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
<td></td>
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<tr>
<td>Fc</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
<td>t = 1.03</td>
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<td>*p &gt; 0.3</td>
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<tr>
<td>Ga</td>
<td>t = 7.1</td>
<td>Ø</td>
<td>Ø</td>
<td>t = 13.2</td>
<td>Ø</td>
<td>Ø</td>
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<tr>
<td></td>
<td>*p &lt; 0.001</td>
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<td></td>
<td>0.001</td>
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<tr>
<td>Gb</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
<td>t = 0.4</td>
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<td></td>
<td>*p &gt; 0.6</td>
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<td>0.001</td>
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<tr>
<td>Gc</td>
<td>Ø</td>
<td>Ø</td>
<td>Ø</td>
<td>t = 2.97</td>
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<td>*p &lt; 0.01</td>
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<td></td>
<td></td>
<td>0.001</td>
<td></td>
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</tbody>
</table>

* For description of groups see Table 1.
** Not compared.

In contrast, the older animals treated with either 20 or 50 IU of HCG daily (Table 1 Fb, c) did not show a significant response to the injected hormone (Table 2).

The histological picture of the implants in animals receiving FSH or PMSG consisted mainly of corpora lutea and a small number of primary and Graafian follicles. In a few single cases more developed follicles and small cysts could be seen.

Histological pictures of the implants in rats treated with GH did not differ from those in the control animals, while after LH, P and HCG a more pro-
nounced tendency to luteinization was evident. Histologically, the ovary in situ always resembled the implant in all the animals treated with various hormones.

It should be noted that the weights of ovaries in situ of the animals treated with LH (Table 1C) and FSH (Table 1D) were almost identical and much higher than in the hemicastrated control rats (Table 3). NIH-P (Table 1E) caused a slight but significant (Table 3) increase of the mean ovarian weight, while the very small increase noticed in animals treated with GH (Table 1B) was not statistically significant (Table 3).

The highest mean weight of the ovary in situ was observed in rats treated with PMSG (Table 1G), the results obtained being highly significant in comparison with the control animals, especially in the younger age group and in the older animals injected with 50 IU daily (Table 3). HCG caused a much smaller increase in the mean weight of the ovary in situ (Table 1F), which in the older age group treated with 20 IU daily, was not even statistically significant (Table 3).

As the weight of the uterus in hemicastrated control animals varied according to the functional state of the ovary in situ, differences between control and hormone-treated animals would be difficult to interpret and, hence in this respect, no comparisons were made. It should be noted, however, that in animals treated with FSH, PMSG, LH and HCG the uteri were much larger than in the untreated animals or in those treated with either GH or P.

**Discussion**

The cause of the arrest of growth of the »dormant« implants is not well understood. It may be ascribed either to an insufficient rise in the gonadotrophin level in hemicastrated animals as compared to castrated ones (Edgren et al. 1965; McLaren 1966) or to the »consumption« of gonadotrophin by the ovary in situ (Bruzzone et al. 1952; Gans 1950; McLaren 1966; Wijnans 1954) to such an extent that the remaining amounts are not sufficient to promote the growth of the implant. It has also been suggested that the amount of gonadotrophins reaching the implant is sufficient to promote its growth, but that oestrogens or other hypothetical factors (Li & Gardner 1949) produced by the ovary in situ inhibit the growth promoting influence of gonadotrophins, acting directly on the graft.

If the lack of sufficient amounts of gonadotrophins available to the implant is responsible for the arrest of its growth, one would expect a weight increase following the daily injections of gonadotrophins. The present results showed that P did not exert any influence on the implants, in agreement with the results obtained by other investigators (Biskind et al. 1953; Fels et al. 1965). LH and HCG caused only a very slight increase indicating that lack of LH is probably

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### Table 3.
Statistical analysis of the differences of the mean weight of ovaries between experimental and control rats.

<table>
<thead>
<tr>
<th>Groups compared</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>Fa</th>
<th>Fb</th>
<th>Fc</th>
<th>Ga</th>
<th>Gb</th>
<th>Gc</th>
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</tbody>
</table>

* For description of groups see Table 1.

** Not compared.
not the cause of growth retardation of the graft. In agreement with this is the fact that after injections of FSH or PMSG, which contain only very small amounts of LH, a massive luteinization occurred in the implants probably under the influence of endogenous LH. A release of LH from the pituitary of rats and mice was observed by many investigators after treatment with FSH (Meyer & McCormack 1967; Selye 1947; Zarrow & Gallo 1966) or PMSG (Callantine & Humphrey 1965; Fluhmann 1939; Fuller et al. 1968; Klausing & Meyer 1968; Li & Gardner 1949; Wagner 1968). It cannot be excluded, however, that the small amounts of LH contaminating the FSH or PMSG preparations is sufficient to produce luteinization by acting directly on the ovarian tissues (Aron et al. 1969; Browning et al. 1965; Browning & Larke 1965).

In contrast to LH, preparations of both FSH and PMSG caused a considerable growth of the implants. These results differ from those of Biskind et al. (1953) who did not find any effect by PMSG on spleen-ovaries in hemicastrated young mature rats injected intraperitoneally three times weekly with 5 IU. This lack of agreement may be ascribed either to the different techniques used by them or to the age-related different degree of reactivity of the animals. In older rats, alongside with the decreasing intrinsic property of ovarian tissue to grow (Ber 1968b, 1970a), the amount of PMSG necessary even for a slight stimulation of the growth of »dormant« implants must be considerably raised, as can be deduced from a comparison of the results obtained in groups Ga, Gb and Gc (Table 1).

The higher mean weight of the implants obtained with PMSG (Table 1 Ga) than with FSH (Table 1D) may be attributed to the better development of grafts in younger animals (Ber 1968b). The ratio of the mean weight of the implant in experimental animals to that in bilaterally castrated control rats of corresponding age (Table 1 Ha, Hb) indicates that the values obtained with FSH were even somewhat higher than those after PMSG.

The results obtained by us with the various gonadotrophins could be interpreted as indicating that the pituitary of the hemicastrated rats produces amounts of FSH insufficient for the development of Graafian follicles. A lack of sufficient FSH-priming could also explain why the presumably normal amounts of endogenous LH or injections of LH or HCG could not induce a massive luteinization and consequently a considerable stimulation of the growth of the implant.

The smaller growth of the implants in animals treated with very large doses of FSH (Table 1D) or PMSG (Table 1G), as compared to bilaterally castrated control rats (Table 1H), could be explained by the fact that the preparations used are substances alien to the rats, thus inducing an immunological response and hence, a declining influence with time (Fluhmann 1939; Freud & Uylbert 1947; Land & McLaren 1967; Talaat & Laurence 1969). It could also be assumed that the rhythm of the administration of the exogenous gonadotrophins, differ-
ing from the continuous release of gonadotrophins from the pituitary of ovariec-
tomized animals, may be responsible for their weaker activity.

All these suppositions, however, do not answer the principal question as to
why the ovary in situ grows significantly under the influence of injected LH
or HCG (Table 1C, F) while the implant does not. If the amount of endogenous
FSH is not sufficient to influence the development of follicles in the implants
to such an extent as to respond to injections of LH, why is it adequate to affect
the reactivity of the ovary in situ? Since it is not likely that the ovarian cells in
the implants are less susceptible to gonadotrophins than the cells of the ovary
in situ, the supposition that inadequate amounts of FSH produced by the pi-
tuitary of the hemicastrated rat are responsible for the lack of growth of the
»dormant« implants should be dismissed.

The assumption that the ovary in situ consumes gonadotrophins to such an
extent that the hormone is not available to the implant seems, at first sight, to
be compatible with all the facts observed. The existence of such a regulatory
mechanism is, however, strongly criticized by many investigators (Greenwald
1968; Selye 1947). Furthermore, in our experiments, this could not explain the
fact that 20 IU of PMSG in the younger animals caused a considerable growth
of both the ovary in situ and the implant (Table 1Ga) while in older rats only
the ovary reacted (Table 1Gb). Since it seems unlikely that an ovary with a
smaller intrinsic growth capacity consumes more FSH than the faster growing
ovary, the »consumption« theory should also be abandoned. Therefore, the sup-
position that a substance(s) produced by the ovary in situ may interfere with the
gonadotrophic influence at the level of the implant remains at present the most
acceptable possibility.

The possibility that oestrogens might inhibit the gonadotrophic action on the
implant (Heller & Jungck 1947; Kullander 1956; Li & Gardner 1949) seems to
us not to be well founded. In experiments performed by us (unpublished) on
chemically hypophysectomized rats (with the pituitary inhibitor metallibure,
I.C.I. 33.828 – Walpole 1965), injections of gonadotrophins together with
oestrogens exhibited a better development of the implants than gonadotrophins
alone. Observations made by other investigators (Bradbury 1961; Croes-Buth
et al. 1959; Pencharz 1940; Smith 1961; Williams 1940; Young 1961) on hypo-
physectomized or infantile rats treated with gonadotrophins have also shown
that the addition of oestrogens enhanced the growth of the ovaries in situ. These
findings together with observations formerly discussed by us (Ber 1968a) lead
us to suggest that the substance(s) produced by the ovary is different from
oestrogen (Ber 1968a; Li & Gardner 1949). Its nature is still obscure but it could
be assumed to belong to the group of growth-inhibiting substances (chalones?
retine?) found in various tissues (Armstrong & Greep 1965; Bardos et al. 1968;
Bullough 1964; Wright 1969) resembling, probably, those produced by the left
ovary of the hen (Gardner et al. 1964) or by the gonad of Ambystoma

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(Humphrey 1942) which inhibits the development of the contralateral gonad.

The inhibiting influence of the hypothetic substance may to some extent be diminished by using very large amounts of FSH. This suggests a relation of a quantitative nature between the gonadotrophin-inhibiting substance and gonadotrophin, and, possibly, a competition for a common binding site.

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