LAWS OF GROWTH OF MAMMARY GLAND TISSUES IN IN VIVO CULTURE

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Because of its histophysiological properties, the mammary gland occupies a special place in the series of the glandular organs. Its external secretion takes place in association with the activity of various glands of internal secretion.

It has been claimed that proliferation of the mammary gland is caused by ovarian hormones [5, 15], even if applied locally [18]. This view is shared by D. I. Golovin [2], who observed more intensive inflammatory proliferation of the epithelium of the mammary gland in the pregnant female, and by M. M. Averbakh [1], who studied age changees in the connective tissue of the gland associated with the influence of sex hormones.

Some workers maintain [8, 13, 17] that the sex organs act upon the mammary gland only through the hypophysis. Some also claim [7,12,14] that the hormones of the hypophysis are of great importance to the vital activity of the mammary gland. During pregnancy the mammogenic function of the hypophysis may be taken over by the placenta [3]. Other workers [4], however, deny that the sex hormones are concerned in the production of the mammogenic hormones of the hypophysis. The regeneration of the nipple [9, 10, 11] also reflects hormonal changes in the organism.

All authorities thus recognize that the mammary gland functions in association with the activity of the glands of internal secretion; the differences of opinion are concerned only with specific aspects of the influence of individual hormones.

In order to elucidate the relationship between growth of the mammary gland tissue and hormonal influences, we used the method of cultivation of tissues and organs in vivo as developed by F. M. Lazarenko [4], used for the first time to study the mammary gland.

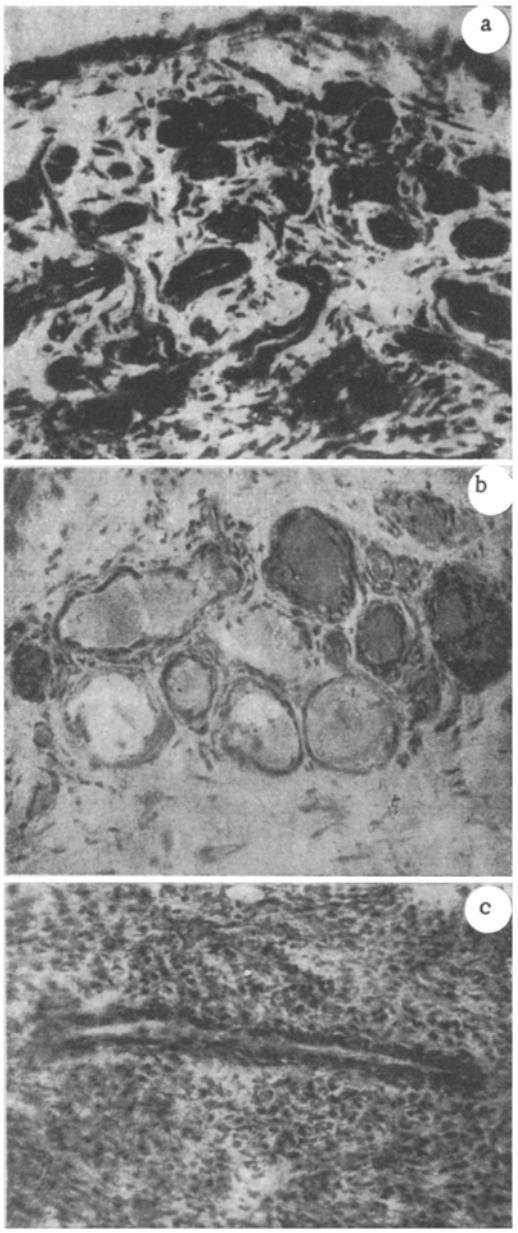
EXPERIMENTAL METHOD

Experiments were carried out on dogs. The donors and recipients were fully grown animals. The recipients were divided into 4 groups: (1) nonpregnant females with intact ovaries, (2) nonpregnant females from which the ovaries had been removed, (3) pregnant, and (4) nonpregnant hypophysectomized dogs. The implants were extirpated between 2 and 60 days after the beginning of the experiment, fixed in Zenker's formol, and embedded in celloidin. Sections were stained with hematoxylin and eosin.

EXPERIMENTAL RESULTS

The epithelium of the parenchyma of the mammary gland of the donor, implanted into the recipients of the first and second groups, showed no signs of growth and died within the first 2 days. The corresponding epithelium in the recipients of the third group grew successfully and revealed its histophysiological properties.

The glandular epithelium began to grow not only from monoepithelial cells, as hitherto considered, but also from differentiated secreting cells. On the first day of implantation the differentiated epithelial cells of the donor's gland passed into a state characteristic of inflammation, and on the 2nd day they began to proliferate along with myoepithelial cells. Both types of cells proliferated on the spot. Alveoli and ducts were obliterated and converted into epithelial bands. A similar state of activation and growth was seen in the connective tissue and endothelium of the small vessels of the fragment of donor's gland and the recipient's tissue surrounding the implant. The connective-tissue framework of the implant was formed from tissues of both the recipient (principally) and the donor. In this



Culture of the mammary gland in vivo on the 4th day (a), 15th day (b), and 12th day (c). Stained with Weigert's hematoxylin and eosin. Eye-piece 2X, objective 40X.

framework were arranged pieces of implanted gland with epithelial bands replacing the original alveoli. On the 3rd or 4th day of implantation these bands invaded not only the true connective tissue of the implant, but also the new connective tissue of the intercelloidin septa.

On the 5th-6th day spaces appeared in the bands as a result of redistribution of the cells (see figure, a) and the structure began to resemble that of a complex tubular gland. On the 8th day of implantation the system of branching tubes formed a lobule of the gland very similar to the lobule of the normal organ. The lobules consisted initially of tubes lined with a double layer of nonsecreting epithelium.

The period of formation and existence of the nonlactating lobules of the gland was sometimes prolonged, depending not only on the phase of inflammation in the region of the implant, which is all-important in the case of other epithelial organs, but also on the hormonal interrelationships in the body of the recipient.

The lobules of the gland in the implant entered the secretory period (see figure, b) at the same time as the recipient's own gland, namely at the end of pregnancy or on the first day after parturition. While secretion was taking place from the lobules in the implant, other lobules were formed from undifferentiated elements. The mass of new glandular tissue increased. The newly formed lobules of the gland had no efferent ducts. They consisted of round or elongated sacs, filled with secretion. Under pressure of this secretion some alveoli were greatly distended and had ruptured. The secretion escaped into the connective tissue and the alveolar walls could then be repaired.

The cessation of secretion, however, was not dependent on the phase of inflammation, as is characteristic of cultures of exogenous glands, but on the hormonal conditions created in the body of the recipient.

After removal of the young from the recipient mother dog at the height of lactation, regression of the lobules of the mammary gland began to occur in the implant. The alveoli were strongly distended with secretion. Their epithelium became flattened and died, while the lobules of the gland diminished in size. Narrow nonsecreting tubes, corresponding to lacteals, persisted in the lobules. Meanwhile similar processes of involution took place in the recipient's own gland.

Hence, the hormonal interrelationships created in the pregnant and lactating female recipient regulated the growth, function, and involution of the donor's glandular tissue as well as of its own mammary gland. The donor's mammary gland tissue in the implant were modified in a similar manner to the tissue of the new host (the recipient).

After implantation of the mammary gland into the recipients of the fourth group – nonpregnant hypophysectomized females – the epithelium grew both in the implant itself and in the surrounding connective tissue of the intercelloidin septa, but the growth of the epithelium in these animals showed certain peculiarities. Here, as in the pregnant females, epithelial bands were formed. They did not isolate the celloidin, but invaded the tissue of the intercelloidin septa and ramified. Later, as a result of redistribution of the cells or death of the central cells of the band,

spaces were formed in the bands, which were converted into tubes, either empty (see figure, c) or filled with detritus.

On the 6th-8th day of implantation the epithelium of the tubes became double-layered with no sign of secretion. If the epithelium in any part of the tube lay on particularly young connective tissue, it gave rise to new growth buds, while a more highly differentiated epithelium was present in other parts of the tube. Growth of the epithelium in the implants of the hypophysectomized recipients terminated when the inflammation in the implant subsided and the loose connective tissue was converted into compact.

Hence, in the nonpregnant hypophysectomized recipients, the factor inhibiting growth of the implanted mammary gland tissues was removed. In these conditions, growth of the mammary gland epithelium of the donor had the character of inflammatory proliferation, such as was unobtainable in the nonpregnant females with an intact hypophysis.

SUMMARY

Mammary gland epithelium from dogs was studied by the method of in vivo tissue culture developed by F. M. Lazarenko. In the implants of nonpregnant recipients with intact or excized ovaries the growth of the donor lacrimal gland epithelium is inhibited. Epithelium of the donor gland grows well according to the inflammatory proliferative type in the implants of hypophysectomized females. In the implants of pregnant recipients new secreting lobules grow from the donor mammary gland epithelium; their function is analogous to that of the recipient's gland proper (in form and time).

Thus, in the process of evolution the lacrimal gland epithelium lost the protective properties of cutaneous epithelium, from which it had originated, and its growth and differentiation became dependent on the body hormonal correlations.

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