Though the incidence may be low, no inbred strain of mice used for experimental studies on mammary cancer has been found to be entirely free from these tumors over a period of years. Other stocks have a high incidence of mammary carcinoma in virgin and/or breeding females. These differences may be a result of variations in:

(a) The inherited susceptibility or resistance of the mammary tissues to the development of spontaneous carcinoma.
(b) The amount of estrogenic stimulation of the mammary glands.
(c) The kind of milk influence obtained while nursing.

It has been assumed that mice of strains with a low incidence of mammary tumors are not susceptible to the spontaneous development of this type of neoplasm. A review of the literature demonstrates, however, that the incidence may be low because animals have:

(a) An active milk influence and are not susceptible.
(b) An inactive milk influence and are not susceptible.
(c) An inactive milk influence and are susceptible.

Tumors which develop in susceptible or nonsusceptible mammary tissues may have the same histological structure, but as the inherited characteristics of the mammary glands are not identical their growths may, perhaps, result from different causes. How may these differences be demonstrated?

By observing the incidence of mammary tumors in the progeny of cancerous (and some noncancerous) mothers, it is possible to differentiate the types of mammary neoplasms arising in mice of inbred strains. In making these comparisons only those data obtained from animals subjected to normal breeding will be considered. The probable roles played by forced breeding and the administration of estrogenic hormones have been presented.

In an inbred strain of mice with a high incidence of mammary cancer, Strong showed that there was no apparent difference between an animal which developed a tumor and one which did not. The progeny of noncancerous animals had a high tumor incidence. These observations have been confirmed on other high tumor strains.

In the milk of females from high cancer stocks there is an active milk influence which they transfer while nursing; the influence in the milk of females from low cancer strains is usually inactive in the etiology of mammary cancer. This active milk influence may arise in mice which have not been in contact with animals having a high incidence of mammary tumors and so it would be possible for mice with a low incidence of mammary tumors to transfer the active milk influence. If these mice were used to nurse animals which had inherited the susceptibility for spontaneous mammary cancer, a high incidence of tumors would be found in these susceptible mice.

When the young born to females from high cancer strains of mice were given soon after birth to foster mothers of low cancer strains with the inactive milk influence, the incidence of mammary tumors in these fostered mice was very low. A few of the fostered mice which remained with their maternal parents of the high cancer stock for not longer than 24 hours before they were fostered developed mammary tumors. Many of their progeny and descendants did, also, but the incidence in these mice was not so high as in the controls (unfostered mice of the high cancer stock). A few fostered females without cancer, usually members of litters having one or more females with cancer, also had offspring that developed cancer but the incidence was not so high as in the progeny of the cancerous fostered mothers. Few of the progeny of the fostered mice that remained free of cancer developed mammary tumors. If any of the descendants of these fostered noncancerous mice developed mammary tumors their progeny had a low incidence, as did the progeny of their noncancerous litter mates. However, one female gave rise to a line with a high incidence.

If the young born to fostered noncancerous females or their descendants were not permitted to nurse their maternal parents, but were given to females of a high cancer stock with an active milk influence, a high
incidence of mammary tumors resulted (8). Thus foster nursing of mice from high cancer stocks does not change the inherited susceptibility of the fostered mice and their progeny to the development of spontaneous mammary tumors (11, 13, 14).

It is possible for a line (Ax) of mice descended from a fostered female of a high cancer stock (A) and having a low incidence of mammary tumors (4.5 per cent) to change to a high cancer (AxT) strain (96 per cent) without contact (nursing, etc.) with mice of a high cancer stock (11, 13). Also, females of the AxT strain which were free of cancer bore progeny of which a high percentage developed mammary tumors. Whereas the mice of the fostered Ax stock when weaned were shown to have an inactive milk influence, the mice of the AxT strain had an active milk influence (9, 13). They reacted in the same way as mice of the control or unfostered A stock.

Breeding females of the C57 black stock (17) and their hybrids, having and nursing maternal parents from this strain, had a low incidence of mammary tumors (6, 15). The hybrids and backcross generation animals gave evidence that mice of the C57 black stock were not susceptible to spontaneous mammary tumors (15).

Mice of the C57 black stock nursed by females of the high cancer C3H stock had an incidence of 10.3 per cent (1); when nursed by females of the high cancer A stock the fostered mice and their progeny had an incidence of 10.6 per cent (10). The progeny of the fostered cancerous mice of the C57 stock had the same incidence of mammary carcinoma as did the progeny of the fostered noncancerous females. When these nonsusceptible fostered mice of the C57 stock were used to nurse mice which were susceptible to mammary tumors, the susceptible animals had a high incidence (10).

Andervont (2) found that breeding females of the C stock have an incidence of 2 per cent. A high incidence was observed in mice of the C stock fostered by females of the high cancer C3H stock (3) and also among the progeny of the fostered mice which died without having developed mammary cancer (personal communication).

**DISCUSSION**

By observations on the incidence of mammary tumors in the progeny of cancerous and noncancerous mothers at least two types of tumors may be distinguished. These may be termed the inherited and noninherited types. It is possible that the exciting influences responsible for the production of these tumors are not identical (7).

Before mammary carcinoma can arise the gland must undergo development from stimulation of the estrogenic hormones. The amount of hormone produced in virgin females of different strains of mice is probably determined by intrinsic factors (19) and is not causally related to the incidence of mammary cancer. In breeding females, on the other hand, an amount of hormone is assured which is adequate to produce growth of the mammary tissue and accordingly to permit the cancerous change to occur when the other etiological influences are active. Thus the difference between the inherited and the noninherited type of mammary tumor in breeding females must be a result of variations in the character and concentration of the mammary tumor-milk influence and/or the intrinsic susceptibility or resistance of the mammary glands.

Mice of strains with a low incidence of mammary tumors may be susceptible (2) or nonsusceptible (6, 13, 15, 17) to spontaneous tumors.

If mice of susceptible strains are nursed by females with the active milk influence, a high incidence of mammary tumors will result in the progeny of these fostered mice whether they die with cancer or without. Under these conditions the growths would be termed "inherited tumors," whereas those arising in unfostered animals with an inactive milk influence would belong to the "noninherited" group.

Mammary tumors appearing in unfostered (inactive milk influence) and fostered (active milk influence) mice of nonsusceptible strains would be noninherited growths, as cancerous and noncancerous females would have progeny with a low incidence. While the active milk influence obtained from females of high cancer strains is able to overcome the threshold of nonsusceptibility of the mammary glands in only a few of the fostered animals, if the fostered mice are used to nurse mice susceptible to the development of spontaneous tumors a high incidence will result in these susceptible mice (10).

High cancer strains of mice may become low cancer strains by foster nursing to females of low cancer stocks having an inactive milk influence (4). This does not change the inherited susceptibility of the fostered mice and their progeny to the development of spontaneous tumors (14).

If the offspring of females of high cancer stocks are transferred before they have received any of the active milk influence from their potentially cancerous mothers, they and their progeny will have a low incidence and the tumors which develop will usually be not inherited. If the fostered mice obtain a small amount of active milk influence from their maternal parents before they are fostered they may develop cancer and bear cancerous progeny. The incidence of
cancer among the progeny will not be as high as that in the unfostered stock (8). In confirmation of recent observations (13, 15), the incidence was higher for those born in successive litters, which indicates that the concentration of milk influence increased with the age of the mothers and that the incidence of mammary tumors and the average tumor age may be partly determined by the amount of active milk influence received (9).

Inherited mammary tumors will result if the progeny of these fostered mice receive the active milk influence as the result of nursing (8). This influence may arise without contact with mice of high cancer strains (11). The amount of the active influence may be greater in the milk of females of some high cancer strains (18).

Thus there have been recognized three inciting influences in the production of spontaneous mammary tumors in mice. Since these will not arise in undeveloped mammary glands, the estrogenic stimulus must be considered as the primary inciting influence. While the estrogens will elicit the growth of mammary tissue, the architecture of the glands apparently is determined by the type of milk influence received while nursing (21, 19) and by intrinsic factors (21).

The feeding or injection of material containing the second influence, an active milk influence, produced few tumors when given to breeding females which had received inactive milk influence while nursing (Duran-Reynals and Bittner, unpublished). This suggests that if the architecture of the mammary tissue is established on the basis of an inactive milk influence, the addition of an active milk influence is unable so to alter this arrangement as to result in the formation of tumors.

The third influence is the genetic susceptibility or nonsusceptibility of the mammary tissue to the development of spontaneous mammary tumors (6, 7, 15). This is an inherited character, and genetic susceptibility may be transmitted by males and females of a susceptible stock.

The inherited type of mammary tumors develops in animals having all the active inciting influences. Noninherited mammary tumors arise in mice which receive the inactive milk influence and are susceptible or nonsusceptible, and in animals which have the active milk influence and are not susceptible to the development of mammary cancer.

It was decided several years ago to use the term "influence" (4) for the active principle in the milk of high cancer strains which plays an important role in the development of mammary cancer, until the nature of this agent had been determined. It has also been called the mammary tumor inciter (MTI) (22) and the cancer-inciting influence (2).

As it appears (7–16) that there must be at least three "inciting influences" active in the development of the inherited type of spontaneous mammary tumors in mice, it is improbable that any single influence can be considered as "the mammary tumor inciter." If one or more of the influences are inactive, a low incidence of mammary tumors usually results.

On the basis of the data available at the present time it is impossible to state if any one influence should be considered as the active mammary tumor inciter. The initial stimulus to the development of mammary cancer in mice takes place when the mammary glands start to develop as the result of estrogenic stimulation. This might be termed a "preparatory influence" in the development of mammary tumors. If it be so, the amount of estrogenic stimulation may determine the incidence and average age at which tumors will appear, a small amount resulting in a low incidence and a late tumor age and a large amount in a high incidence and an early tumor age (16). Furthermore, the amount of estrogenic stimulation produced in virgin females of various strains is probably the result of intrinsic differences and is not causally related to the incidence of mammary tumors (19).

The architecture of a precancerous gland is determined by the active milk influence and intrinsic factors (21, 19), but for a high incidence the active milk influence must be present when the glands are in the initial stages of development. As the estrogens must prepare the mammary tissues to become cancerous, so must the milk influence, and probably also the inherited susceptibility. Thus, all the active influences may be called preparatory influences, but as they are complementary influences they may be considered as mammary tumor inciters.

If the various influences or inciters are to be differentiated and given symbols, a distinction should be made between these various agents or factors. The active influence (stimulus, agent, factor, or principle?) in the milk from females of high cancer strains might be called the mammary tumor milk inciter (MTMI); the inherited factor (or factors) needed for susceptibility, the mammary tumor inherited inciter (MTII) or the mammary tumor susceptibility inciter (MTSI); and the hormonal influence, the mammary tumor estrogenic inciter (MTEI).

The MTMI would be a noninherited influence or inciter, the MTII or MTSI an inherited inciter, and the MTEI an intrinsic inciter in virgin females which may be supplemented by increased amounts resulting from extrinsic influences (breeding and injection).

The only purpose of these symbols would be to simplify reference to the various influences responsible for the development of mammary tumors. If they should be used in an attempt to express the concentra-
tion or the amount of stimulation of some influences resulting from intrinsic and/or extrinsic causes, only confusion on the part of the reader would be the result.

SUMMARY

Observations on the incidence of mammary tumors in the progeny of cancerous and noncancerous mice indicate that there may be at least two types of mammary tumors—inhherited and noninherited.

The inherited type develops in mice which receive active milk influence and are susceptible to the development of spontaneous growth.

Noninherited mammary tumors arise in animals which receive active milk influence and are nonsusceptible or which receive inactive milk influence and are either susceptible or nonsusceptible to spontaneous tumors.

There are probably three mammary tumor inciters—the mammary tumor milk inciter (extrinsic); the mammary tumor estrogenic inciter (intrinsic and extrinsic); and the mammary tumor inherited inciter (intrinsic).

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Possible Types of Mammary Gland Tumors in Mice

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