organic lesion, such as cancer, which may escape attention because the attending physician, in evaluating the symptoms, may be biased by knowledge of the neurotic personality of the patient. It should therefore always be borne in mind that before a diagnosis of gastrointestinal neurosis is arrived at, every possibility of organic diseases such as cancer and gallstones should be ruled out by the proper examinations.

SUMMARY

1. The relationship of personality disorders to gastro-intestinal diseases is outlined.

2. The symbolism of organ language in digestive tract diseases is described.

3. Analysis of patients with the spastic "colitis" or spastic colon syndrome is presented from the psychosomatic aspects.

4. Biochemical and physiological studies are demonstrated in so-called "nervous indigestion," showing the biologic changes occurring in various psychosomatic disturbances affecting the gastro-intestinal tract.

6333 Wilshire Boulevard.

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Breast Cancer in Mice

MICHAEL B. SHIMKIN, M.D., *San Francisco*

ONE of the earliest published descriptions of a mammary tumor in a mouse was made by Crisp in 1854. Scattered descriptions of a few tumors appeared in the literature between 1891 and 1906 in connection with experiments being carried on during that period in transplantation of tumors. Apolant, in 1906 made a noteworthy contribution in his exhaustive and accurate description, classification, and consideration of pathogenesis, based on the study of 276 tumors. Additional studies by Borrel, Michaelis, J. A. Murray, Haaland, and others permitted the conclusion that these tumors are malignant epithelial new growths of the mouse.

Mammary tumors in mice originate multicentrically from the cells of the mammary epithelium. The tumors may arise from any portion of the mammary tissue, which in the mouse extends over the whole subcutaneous area from behind the ears to the base of the tail except for small midline ventral and dorsal strips. The subcutaneous tumors grow progressively, and spontaneous regression is rare although by no means unknown.

Microscopically, numerous morphologic variations between different tumors and different areas of the same tumor are encountered. Although in the majority an adenomatous pattern revealing its relation to or derivation from glandular structure is evident, arrangement may be in compact masses; and papillary, cystic, and hemorrhagic areas also are frequent. More rarely, keratinizing and molluscoid forms may be seen, and a few tumors contain neoplastic connective tissue elements as well, forming carcinosarcomas. Despite these variations, however, the tumors form a pathologic entity, and for most purposes the term "mammary tumor" is adequate.

The mammary tumors invade and infiltrate contiguous tissue, metastasize to the lungs and other sites, and recur after incomplete removal. The neoplasms can be transplanted into mice of the same genetic constitution, and some grow heterologously in the anterior chamber of the eye of rabbits or guinea pigs. The tumors grow in tissue culture and can be cultivated in the yolk sac of the embryonic chick.

On the whole, the biochemical constituents of mammary tumors are very similar to those of other mouse tumors. There is an accumulation of lactic acid, a lower pH, and a higher rate of anaerobic glycolysis than in most normal tissues. The vitamin concentration is near the upper level seen in other tumors, and the pattern of enzymes is similar to that in other mouse tumors. The values for the esterase of

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The reader is referred to "A Symposium on Mammary Tumors in Mice," by members of the Staff of the National Cancer Institute, Am. Assn. Advancement Sc. Publ. 22, 1945, and to Shimkin, M. B., Experimental Induction of Mammary Cancer, Surgery 19:1-24 (Jan.), 1946, for fuller treatment and bibliography on the subject.

Surgeon, United States Public Health Service. Director, Laboratory of Experimental Oncology, University of California Medical School, San Francisco, California.

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the blood serum, the catalase activity of the liver and kidney, and the hemoglobin of the blood are lowered with growing tumors.

Soon after the inception of cancer research on mice, it was noted that tumors appeared more often within certain cages of the colonies than within others. The immediate response to the observations of this selective occurrence of tumors was the suggestion of an infectious origin, particularly stressed by Borrel. In opposition to this theory, Loeb's studies suggested that hereditary factors were involved, and this concept was strengthened by the experiments of several investigators. J. A. Murray's paper of 1911 presented convincing evidence that female mice in whose immediate ancestry cancer of the breast occurred, were distinctly more liable to develop the disease than mice in whose ancestry tumors were more remote. The experiments of Lathrop and Loeb and of Slye further demonstrated that hereditary factors influenced the formation of tumors. As early as 1909, Little foresaw that homozygous strains were essential for an adequate analysis of characters as complicated as tumors. Experiments with homozygous strains of mice with incidences of mammary tumors ranging from less than 1 to over 90 per cent, developed by Little, Strong, and other geneticists, did not allow postulations of any simple genetic transmission of mammary or other tumors and also showed that degrees of susceptibility to different types of tumors are inherited as separate characters.

It is now established that susceptibility to mammary tumors is not a character with an all-or-none expression but is expressed in degree. Genetic factors influencing susceptibility are multiple. There is a relationship between mammary tumor development and a known, inherited, single-factor, coat-color trait —lethal yellow.

THE ROLE OF HORMONES

The experimental demonstration of the influence of ovarian hormones on the development of mammary tumors in mice was begun in 1913 by the work of Loeb and his associates. It was found that mammary tumors occurred more frequently in breeding than in non-breeding mice. Loeb further demonstrated that the incidence of tumors can be radically reduced by ovariectomy, and that the incidence is related to the age of the animal at the time of ovariectomy. Cori and W. S. Murray substantiated these findings, and the latter succeeded in obtaining mammary tumors in castrated male mice bearing ovarian grafts.

With the advent of chemically isolated estrogens, Lacassagne in 1932 reported the appearance of mammary tumors in male mice injected with these compounds. Most important was the fact that estrogens would elicit mammary tumors in males of strains in which females developed such tumors spontaneously, and in approximately the same incidence. Males of strains in which the tumor incidence was extremely low did not develop mammary cancer despite strenuous treatment with estrogens.

Development of mammary carcinomas has been elicited in male mice of susceptible strains with all the natural and synthetic estrogenic compounds that have been studied. The list includes estrone, estradiol, estriol, equilin, equilenin and their benzoates, diethylstilbestrol and its dipropionate, and triphenylethylene. In general, the carcinogenic activity tended to be related to the amount of estrogen in physiologic units rather than to chemical configuration or other properties. The chemicals could be administered subcutaneously, percutaneously, or orally with the same results, depending on the physiologic activity by the particular route. However, they had to be administered for some length of time, eight weeks or longer, for tumors to appear at a subsequent date. With the compounds in oily or aqueous media, having short periods of activity due to rapid elimination, relatively heavy doses were required to elicit the carcinogenic reaction. When the compounds were given in the form of subcutaneously implanted pellets, allowing steady and constant absorption, it was found that the dose of estrogen needed for the induction of mammary tumors was not above that physiologically elaborated by untreated female mice.

These experiments also permitted a thorough microscopic study of the changes in the breast leading to neoplasia.

In the male or the ovariectomized immature female with an intact pituitary, the mammary gland is a rudimentary structure of a few stunted ducts. The ducts begin to proliferate and to dilate within a few days after the administration of estrogens. They soon form buds, and the cells of the proliferating epithelium are large, with clear cytoplasm and vesicular nuclei. In some ducts, the cells become arranged in several layers and secrete an acidophilic product in the form of intracellular and extracellular droplets. The process progresses to the formation of small acinous lobules, so that the rudimentary breast becomes as well developed as that in the normal female. With excessive doses of estrogen, however, the glands become stunted and have localized areas of extensive alveolar development. If estrogen is discontinued at this point, the mammary hyperplasia undergoes gradual regression. With continued estrogenation, there is progressive hyperplasia of the alveoli and ducts; dilation of the ducts, round-cell infiltration, and increase in periductal fibrous tissue are observed inconstantly. In mice of strains in which adenocarcinoma does not develop, the process does not progress beyond this hyperplasia. In mice that develop cancer, there is a multicentric formation of adenomatous nodules which often coalesce, and adenocarcinoma develops in these centers. Microscopic examination does not reveal any sudden alteration which may be designated as the point at which the normal cells become neoplastic. The site, the growth, and the histologic appearance of mammary tumors elicited in mice injected with estrogens correspond in all details to the description of the spontaneous adenocarcinomas in female mice.

Numerous investigations have been performed in an attempt to discover differences in the morphology or physiology of the breast in mice belonging to

strains with different incidences of mammary carcinoma. No clear differences in morphology have been established. In general, however, hyperplasia of the ducts and alveoli under the stimulation of estrogens tends to be more rapid and more uneven, with the eventual development of adenomatous nodules, in the high-mammary-tumor strains. Distention of the ducts into cysts, round-cell infiltration, and an increase in periductal fibrous tissue are inconsistent features apparently not associated with the eventual development of mammary neoplasia.

The morphologic studies also stress that the essential difference between male and female mice, as far as the appearance of mammary carcinoma is concerned, is the practical absence of the mammary gland in the male animals. The formation of the gland and the increase in cellular elements under the stimulation of estrogens thus exteriorize or make possible the development of some factor already present in the animal that leads to the eventual appearance of gross mammary tumors. It is also clear that something more than excess growth is operating in the cancerous transformation of the breast. The onset of recognizable malignant nodules occurs in breeding females or in mice injected previously with estrogens when the major part of the mammary gland is involuting. A difference between the normal growth process and the neoplastic process is also indicated by the unsuccessful attempts to produce a direct transition of the fully developed mammary gland of pregnancy or lactation into a carcinomatous gland by continued injections of large doses of estrogen.

Studies aimed at demonstrating the essential difference between strains of mice that are susceptible to mammary carcinogenesis and those that are not, either spontaneously or under the influence of exogenously supplied estrogens, also took other lines. The estrus cycle of mice of different strains was compared; no correlation was found between the length or regularity of the sexual cycle, duration of keratinization of vaginal mucosa, and the occurrence of tumors. The susceptibility of mice to estrogens, as manifested by the dose required to produce estrus in spayed mice, was not correlated with the susceptibility to formation of tumors. The urinary excretion of estrogens and 17-ketosteroids and the ability of the liver to destroy estradiol in vitro do not differ significantly in the low- and the high-mammary-tumor strains. Nor could correlation be established with degenerative changes in the adrenals, the pituitary, or other endocrine organs.

Although the estrogens maintained their focal point in the genesis of mammary tumors in mice, it was shown that other endocrine secretions, especially those of the adrenal cortex and the anterior pituitary, were involved. Androgens, given over protracted periods of time, reduce the incidence of such tumors. The action is probably analogous to castration, since androgens suppress the estrus cycle and prevent follicular maturation. The adrenal cortex, in relation to sexual functions, can be considered as a potentially bisexual accessory gland capable of secreting either estrogens or androgens under the influence of stimuli from the pituitary gland. Woolley demonstrated that gonadectomy of young mice of two high-tumor strains led to progressive hyperplasia of the adrenal cortex. There was gradual recovery of the uterus, vagina, and breast from the castrate state, and mammary tumors developed in the females. In strains that do not develop mammary tumors spontaneously, no mammary tumors were obtained. Mammary carcinogenesis following gonadectomy is probably best explained by the extragenital production of estrogens in the hyperplastic adrenocortical tissue and is dependent upon whether the normal females of the strains develop tumors of the breast. The origin of estrogens in the adrenals was supported by the close morphologic similarity of the cells of the adrenal nodules to lutein-like cells of the ovary.

Subcutaneous graft of the hypophysis raises the incidence of mammary tumors in intact females but does not elicit them in males or ovariectomized females. Thus, the pituitary probably stimulates secretion from the ovary; it does not increase the incidence of tumors in strains of mice that do not develop such tumors spontaneously.

THE EXTRACHROMOSOMAL FACTOR

Between 1930 and 1933 the members of the staff of the Roscoe B. Jackson Memorial Laboratory conducted a number of reciprocal hybridization experiments with the high- and low-tumor strains that they had by that time perfected. The results of these experiments, along with those of Korteweg, led to the discovery of the extrachromosomal factor in mammary-tumor development and opened the door to one of the most fruitful lines of cancer research of the past decade. The discovery was that the hybrid female offspring resulting from the mating of high-tumor-strain females to low-tumor-strain males developed tumors in approximately the same incidence as the female of the high-tumor strain; but when the reciprocal cross was made, that is, low-tumor-strain females were mated with high-tumor-strain males, the tumor incidence of the female offspring was but little greater than in the female of the low-tumor strain.

Since the genetic constitution, including the sex chromosomes, was the same for the two groups of females resulting from reciprocal crosses between two isogenic lines, it was obvious that this effect was not transmitted through the chromosomes. It had to be some extrachromosomal factor which the female was capable of transmitting to her offspring. It appeared that this factor was probably transmitted by one of three possible routes: through the cytoplasm of the egg, through the placenta, or through the milk or other contact with the mother after birth.

Bittner undertook the study of the third possibility, and it was through his work that the factor was primarily revealed. Almost astonishing in its simplicity, the transfer of mice of high-mammary-tumor strains shortly after their birth to foster mothers of low-mammary-tumor strains reduced the occurrence of neoplasms. The low incidence was maintained in subsequent generations; in two strains with a previous

incidence of 80 per cent, animals of the tenth to the twentieth generation after a single interruption of the ingestion of milk from their mothers of high-cancer strain had an incidence of less than 2 per cent. When complete interruption of the milk ingestion could be assured, as by removal of the young from the uterus, even a lower residual rate of tumors was encountered. The basic observation has now been repeated and substantiated in one dozen or more independent laboratories throughout the world.

When low-tumor strains of mice are suckled by foster mothers of high-mammary-tumor strains, there is an increase in the incidence of mammary tumors. Whether this increased incidence is maintained or not depends on the genetic susceptibility of the strain. Strain C mice, possessing this genetic susceptibility, and having less than 2 per cent incidence of mammary tumors, were transformed, after nursing on high-mammary-tumor strain foster mothers, into a line having an incidence of over 80 per cent of tumors in subsequent generations. In contrast, in mice of strain C57 black, having a high genetic resistance to mammary tumors and the milk agent, the incidence may be increased to as high as 75 per cent by foster nursing them on animals possessing the milk agent, yet in subsequent generations the incidence rapidly decreases as the genetic resistance overcomes the milk influence.

It was also established that the induction of mammary tumors in male mice injected with estrogens was also dependent upon whether such animals possessed or did not possess the milk influence. Thus, hormonal stimulation of the breast is ineffective in mice not having the agent carried by milk.

Despite the lack of an adequate, rapid bio-assay technique, so that 12 months or longer is required for any particular determination, and despite the lack of stable preparations of the milk agent, depriving the experimenter of a standard sample of reference, much has been learned concerning the nature and properties of the milk agent.

It is known that the agent is present in the milk of high-mammary-tumor strains throughout the period of lactation, although it may vary in concentration during the reproducive period of the mouse. When the young of a high-tumor strain remain with their mothers for varying periods before being foster nursed by resistant-strain females, the young remaining with their mothers for shorter periods develop fewer tumors and at a later average age than do the young permitted to nurse from their mothers for longer periods. Other work, in which measured amounts of milk for high-tumor-strain females were fed to susceptible young by means of stomach tube, confirmed this dose-response relationship. A single oral administration of 0.1 cc. of high-tumor-strain milk to susceptible young mice produced mammary tumors in over 90 per cent of the animals, some eight months later. Evidently there occurs an event in the first few hours of life which leads to the appearance of mammary cancer months later.

The incidence of tumors later is higher in animals given the milk agent intraperitoneally than in those to which it is given orally. In all experiments with the agent, mammary tumors do not appear with any greater frequency at, or near, the site of injection than in other mammary glands of the animals.

The agent is widely distributed throughout the body of the mouse. Tumors have been produced in susceptible mice following subcutaneous injection of pieces of spleen, lactating mammary gland, and whole blood. Extracts of mammary tumors fed to susceptible mice evoke tumors, a finding demonstrating the presence of the agent in the tumor tissue. The agent does not seem to penetrate through the placenta. Despite its wide distribution throughout the body, the milk agent is apparently not contagious through body contact. Adult mice are more resistant to the milk agent than are those up to six weeks of age. There are pronounced differences in degrees of genetic susceptibility of different strains of mice to the milk agent, and the ability of such strains to transmit the agent.

Material obtained from lactating mammary tissue of high-tumor-strain mice by filtration through Seitz filters is capable of giving rise to mammary tumors in other mice. Desiccation of lactating mammary gland tissue at room temperature resulted in great loss of activity within one week. Extracts of mammary-tumor tissue to which 50 per cent glycerin was added at 8 degrees C. retained activity for nine days, but were inactive 80 days after the procedure. Lyophilized mammary-tumor tissue suspended in water and fed to mice produced tumors. The preparation was still active when tested six months after lyophilization, although the comparative potency with the original material was not determined, but it was inactive one year following the procedure. The agent survived in mammary tumors propagated in the yolk sac of chicken eggs.

The agent is destroyed in mouse milk and mammary tumor extracts heated to 60 degrees C. for 30 minutes. It survives in mouse milk kept at 8 degrees C. for 14 days, is active in extracts of mammary tumors at pH 5.5 to 10.2, but is inactive at pH 4.5. It is not inactivated by acetone or petroleum ether.

ULTRACENTRIFUGATION EXPERIMENTS

Ultracentrifugation experiments showed that the agent when obtained from lactating mammary glands and suspended in distilled water was sedimented at 110,000 times gravity for one hour. Extension of the ultracentrifuge studies revealed that there were two principal components for the active tumor extract. A minimum molecular weight of three to four million was estimated for the macromolecular component, while the faster moving component had a molecular weight of at least five million. The variations of sedimentation rate with concentration indicated an asymmetric particle.

Ultraviolet absorption spectrograms and other tests indicated the presence of a ribose-nucleic acid complex in the material from mammary tumors containing the agent. However, since similar components were present in normal tissues, it is not clear whether

the agent inciting mammary tumors in mice is an altered ribose-nucleic acid complex or whether this complex is merely the carrier of the active agent associated with it.

Rabbit serum obtained following injections of saline extract of mammary tumor or with ultracentrifuge pellet material neutralized fresh mouse mammary tumor extracts in vitro. Intraperitoneal injections of immune rabbit sera protected susceptible mice against the development of mammary tumors following the feeding of active fresh tumor extract. Recently Shabad announced that the milk agent can be detected by a complement fixation reaction.

Filtration and ultracentrifugation experiments show that the milk agent can be transmitted by cell-free material, and its transmission through many generations of mice implies propagation. These features suggest the action of an agent belonging to or related to the viruses. It is similar to known tumor viruses in its specificity for a certain tissue. It is apparently not involved in the genesis of spontaneous pulmonary or hepatic tumors, or of induced tumors of the lung, subcutaneous tissues, testes, uterus, or the pituitary.

It is not known whether the milk agent continues indefinitely in propagable tumors and whether its presence is required for the continued growth of such transplanted tumors. Preliminary investigations indicate that the presence of the milk agent is not necessary for the propagation of an established tumor, unless a latent phase is postulated. Tumor development is not necessary for transmission of the influence from mother or foster mother to offspring; in fact, under ordinary conditions the causal agent is transferred in the absence of recognized tumor, and this transfer continues for many generations. In this respect, the milk agent acts like a latent virus infection.

Up to the present, no changes in the organism have been described following the introduction of the milk agent. The mice are not sick and gain in weight equally as compared with animals without the milk influence. The onset of the estrus cycles and the character of the cycles for the first three months are unaltered. The adrenal changes following estrogen administrations or castration are not influenced by the presence or absence of the milk agent. The agent does not produce consistent and clear-cut alteration of the architecture of the mammary gland.

OTHER FACTORS IN THE GENESIS OF MAMMARY TUMORS IN MICE

The current concept of the etiology of mammary tumors in mice, as expressed by Bittner, is that at least three factors must be present for their development, (1) an inherited susceptibility, (2) hormonal stimulation, and (3) an active agent that is generally transmitted through the milk. All three factors must be present for the genesis of mammary carcinoma.

These three sets of factors, however, by no means exhaust the number of influences that may play a role in the genesis of these tumors. Of these, nutrition has received the greatest attention. Underfeeding of the total balanced diet or of certain essential constituents thereof, such as sulfur-containing amino acids, reduces the occurrence of mammary tumors.

The mere reduction of a balanced ad libitum diet by one-third led to the total suppression of mammary tumors in a highly susceptible strain possessing the milk agent. The mechanism is probably the production of pituitary insufficiency which leads to a lowered level of ovarian secretion and a relative refractoriness of the mammary gland to estrogenic substances.

It has been reported that the incidence of mammary tumors is increased and the average tumor age is decreased in mice kept at an environmental temperature of 68 degrees F. as compared with mice living at a temperature of 91 degrees F. Even such mild environmental changes as crowding or isolating animals are reflected in the incidence and time of appearance of mammary tumors, probably because of the effect of these factors on food consumption and the estrus cycle.

Furthermore, data have been accumulating to the effect that not all mammary tumors in mice are associated with or due to the presence of the milk agent. Perhaps the most striking demonstrations have been with animals injected with methylcholanthrene, a polycyclic hydrocarbon that elicits a variety of tumors in mice at the site of introduction and at distant sites.

In 1939 it was shown that the appearance of mammary tumors was accelerated by methylcholanthrene on the skin of breeding female mice of the dba strain, known to possess the milk agent and genetic susceptibility to mammary tumors. Mammary tumors were not obtained in male mice, nor was the time of appearance of tumors accelerated in nonbreeding mice. Recently mammary tumors have been elicited by percutaneously administered methylcholanthrene in crosses of two genetically susceptible strains deprived of the milk agent.

Strong and his co-workers reported that a single subcutaneous injection of 1 mg. of methylcholanthrene produced mammary tumors in breeding mice of strains that were characterized by a very low incidence of mammary tumors. Such tumors, usually at the site of injection of the hydrocarbon and often mixed with sarcomatous elements, appeared in 45 of 384 females of the NH strain; of 198 untreated breeding mice, none developed tumors. Bonser and Orr in England also reported the appearance of mammary tumors in mice of two strains (IF and CBA) having a very low incidence of tumors in breeding females, following the subcutaneous or intranasal introduction of methylcholanthrene.

The presence of a transmissible agent in the milk of mice of the NH, NHO, and Bonser's CBA strain was excluded by foster-nursing tests. The work suggests that types of stimuli other than the milk agent may produce mammary tumors in mice. The data are not conclusive, however. It is possible that these strains may harbor the agent and not transmit it in

the milk. Experiments in which tumor material and other tissues are injected into and fed to susceptible mice deprived of the agent are indicated for further evidence in this problem.

Andervont made crosses between two genetically susceptible strains of mice that were deprived of the milk agent and obtained mammary tumors in 50 per cent of the animals. Moreover, extracts of 11 tumors were fed to susceptible mice and no tumors of the breast were elicited. It was concluded that even these data did not prove the absence of the milk agent in the genesis of the tumors, although they strongly suggested it.

The occasional occurrence of mammary tumors in mice of genetically resistant strains or in susceptible strains that have been deprived of the agent cannot be considered as demonstrating that the milk agent was excluded in the etiology of the tumors. In the first place, if the milk agent is some abnormal and transmissible constituent that arises from the cells or tissues of the animals, rather than an exogenous virus-like infection, its appearance *de novo* by some process like somatic mutation can be postulated. On the other hand, it is difficult to exclude simpler explanations such as accidental transmission of the agent from other mice by means of blood-sucking insects, or by ingestion of tissues or feces of the agent-harboring animals in the same or nearby cages.

Studies on the genesis of mammary tumors of mice indicate that the neoplastic reaction is the end result of an intricate interplay of at least four factors or complexes of factors:

1. The genetic constitution of the mouse influences mammary tumor development by determining the susceptibility of the mammary tissue to the hormones and the milk agent, by modifying or altering the mechanism of hormonal stimuli, and by determining the animal's resistance to the milk agent and its transmission. Genetic factors influencing this susceptibility are multiple and are expressed in degree. The ability of the animal to propagate the milk agent and susceptibility to mammary carcinoma may be governed by separate sets of genes.

2. Hormonal stimuli are essential for the development of the breast and, as such, at least for the creation of a suitable substrate for the action and interaction of other factors that eventuate in the development of mammary tumors. There is no evidence that the hormonal complex has to be abnormal, either qualitatively or quantitatively, for the genesis of mammary tumors in mice. Alterations induced in the hormonal balance by the addition or withdrawal of estrogens and other hormones modify the processes that lead to the development of tumors.

3. The milk agent, transmitted through the milk of the mother, is necessary for the appearance of most of the mammary tumors in mice. It should be emphasized that the virus nature of this agent is not established. However, if it is a virus, the appearance of mammary tumors would be influenced by variations in the virulence of the agent under various conditions, and its possible latent stages.

4. Various other environmental factors, such as diet, temperature, and overcrowding, also affect the genesis of mammary tumors, probably by modifying the growth and development of tissues and the hormonal secretions of the animals.

It is quite possible that at least some of the mammary tumors may require different or additional factors for their appearance and, conversely, that some mammary tumors do not require the presence of the milk agent and are of entirely different etiology. Our knowledge has now reached the stage where we can control most of the factors while varying the one under consideration. This allows a step-by-step evaluation of each of the factors. The shifting of attention from the genetic to the hormonal and thence to the milk influence has been due more to historical developments than to the established relative importance of these different influences. It is clear, however, that there is no single cause of mammary cancer of the mouse, but that the neoplastic reaction is the end result of a complex interplay between many factors.