Role of estrogenic principle in the etiology of mammary carcinoma

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THE ROLE OF ESTROGENIC PRINCIPLE
IN THE
ETIOLOGY OF MAMMARY CARCINOMA

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INTRODUCTION

"It is difficult to keep one's footing in a stampede and practically impossible to think or plan connectedly in a panic. Therefore, the members of the medical profession as well as the public, who have been caught in the whirlwind sweep of this new medical advance, have lost all sense of proportion, direction and balance whenever the subject of endocrinology is touched on. In spite of the turmoil, real progress can be recorded, often unheard, because of incoherent babble and ballyhoo, which is more vocal than constructive and conservative advances." (33)

In this turmoil of activity there is a growing sense of doubt as to the efficacy of many so-called hormonal preparations, and an increasing suspicion on the part of many that therapeutic use of certain hormones may not only be without demonstrable effect in the course of the condition for which they are administered, but also be distinctly harmful to the patient.

Such a state of doubt has recently arisen in regard to the administration of the ovarian follicular hormone or of any of its derivatives, and several warnings advising against promiscuous use of such estrogenic principles have recently appeared editorially in
medical journals. (23, 30). There seems to be a definite theoretical and experimental basis for the apprehension expressed, as it has been recognized for many years that during pregnancy (when physiologically there is increased production of estrogenic hormone) the growth rate of a breast cancer is increased.

Many experiments on mice will be thoroughly discussed later which seem to show a definite carcinogenic effect from estrogenic principle.

This paper, therefore, will attempt to clarify the situation, to analyze the merits of the work already done, to point out deficiencies in the present knowledge, and to conclude in so far as is possible at this time, whether actual danger threatens the patient treated with sex hormones.
"The endocrine origin of breast tumors rests on the hypothesis that the stimuli to normal growth when active in increased intensity or applied over excessive or irregular periods of time, may result in atypical forms of proliferation. For that reason the facts of the hormone physiology of the normal mammary gland are of basic importance in the study of breast neoplasms." (70)

It is, therefore, important to review the part played by estrogenic hormones in the physiology of the breast. There has been some discussion over the exact nature of this relationship, but the generally accepted view as presented in most textbooks of physiology and endocrinology will be considered.

Wiggers (76) in describing the development of the mammary glands stated:

"The mammary glands undergo no marked changes from birth to adolescence. During prepubescence and puberty, and correlated with the accelerated development of the ovaries a considerable enlargement occurs in the female. This consists essentially of an extensive development of the duct system including the nipples; but the glandular alveoli develop but little. The association with ovulation suggests
that the estrogenic hormones of the ovary may be concerned and this has been made more certain by the demonstration that injections of theelin stimulate proliferation in immature animals and in castrated males as well as females. From this state of pubertal development no further change occurs unless pregnancy supervenes."

During the first half of pregnancy there is rather marked alveolar hyperplasia while during the latter half there is secretory awakening and hypertrophy of the alveoli. The evidence of many investigations has indicated that such preparation is due to an associated action of theelin and progestin (Wiggers, 76).

According to Edgar Allen (2) the simultaneous action of theelin and progestin has been found necessary to produce complete mammary growth in animals other than the guinea pig.

Wiggers (76) asserted that injection of progestin alone does not produce proliferation of secreting epithelium in spayed rabbits, but that simultaneous injection of theelin and progestin does.

The problem, however, is not so simple as this may suggest. Subsequent work has shown that anterior pituitary substance likewise leads to similar proliferation and hypertrophy. However, such an effect may be consid-
ered to be either direct, by action on the breast tissue itself, or indirect, by action on the ovary causing the production of theelin and progestin as it is known to do.

Wiggers dealt with this phase of the problem and concluded that species differences undoubtedly exist. In the rabbit, anterior pituitary factor seems to be effective in the absence of ovaries, while in the guinea pig and rat ovarian factors must be present. The effects of anterior pituitary hormone also seem to depend on the preceding degree of development of the mammary glands; it being generally conceded that pituitary factors cannot be expected to exert any action on wholly undeveloped glandular tissue.

Work of investigators has generally borne out these statements, and in support thereof stands Edgar Allen (2) who stated in part:

"The growth of the mammary gland is primarily dependent on the estrogenic hormones. The primary ducts of the rudimentary mammary glands of males have been found to respond to both theelin and theelol. At the present time the guinea pig is the only species extensively investigated in which a complete growth of the mammary glands (both ducts
and alveoli) may be induced by theelin. The simultaneous action of theelin and progestin has been found necessary to produce complete mammary growth in other animals so far studied."

His statements were amplified further to the effect that:

"a development of small localized lobules of alveoli in addition to the ducts has been observed in the mammary glands of male mice of an inbred strain following injections of theelin over a long period". He interpreted this finding to be indicative that localized areas of the experimentally grown mammary ducts may be more sensitive to stimulation with theelin. In the light of what is to follow this observation is of considerable importance.

Turner and others (74) confirmed the finding that theelin and theelol are capable of stimulating the growth of the duct system of the mammary gland of the rabbit, rat and mouse, and Evans (25) in writing about recent advances in physiology summarized the work done on this subject in very nearly the same manner as did Wiggers.

Thus is described the effect of endocrines on the breast --- so far as physiologic effects are involved.
SUMMARY

1) Theelin or theelol is capable of producing marked proliferation of the duct system in the mammary gland.

2) Progestin (corpus luteum hormone) alone has no effect, but coupled with theelin it produces alveolar hyperplasia as well as extension of the ducts.

3) Only in the guinea pig can theelin alone produce the development of both ducts and alveoli, while in the rabbit, rat and mouse, the combined action of theelin and progestin is required.

4) Allen, however, describes localized areas of alveolar hyperplasia in the mammary gland of the mouse following prolonged injections of theelin. This he interprets as indicative of greater sensitivity to theelin.

5) Anterior pituitary hormones effect breast development only by indirect action on the ovary (except in the rabbit), but the lactogenic hormone produces lactation in a previously developed breast.
STUDIES ON EXPERIMENTAL ANIMALS

Experimental attack upon the pathogenic effects of the female sex hormone upon the breast has followed essentially along three lines.

The first of these was the finding that tar applied to the skin over long periods of time may induce carcinoma. This led to the isolation of certain chemical substances from coal tar showing similar carcinogenic effect. These substances have since been synthesized.

The second line of investigation began with the analysis of the mechanism underlying the sexual cycle. It proceeded to study the place of origin, the function, and the chemical constitution of the hormones dominating in various phases of the cycle.

The third line of investigation began with a study of the significance of ovarian hormones in the development of mammary cancer in mice.

It was not long after the synthesis of the carcinogenic substances present in coal tar before a chemical similarity was found between these substances and the sex hormones, and Kenna,way, Cook and Dodds (according to Loeb, 53) showed that certain of these chemical substances with carcinogenic effect were also capable of producing estrus in the experimental mice.
Further experiments to be described at greater length have shown that "estrogenic hormones are factors in the development of certain kinds of cancer". (Loeb, 53).

I. COAL TAR PRODUCTS AND CANCER

The first series of experiments began with the finding by Yamigawa and Ichikawa in 1915 (79) that long continued applications of tar to the ear skin of rabbits may initiate cancerous changes in the tissue thus exposed to the action of this substance.

Tsutsui (73) in 1918 extended this work by showing that in mice epidermal cancer can be produced in a considerably larger percentage of cases than in rabbits. He thus established the mouse as the more favorable species for testing the carcinogenic power of various substances related to or derived from tar.

Chemical studies by Bloch and Dreifuss (6) next revealed that the compounds present in tar and responsible for the production of cancer are neutral, nitrogen-free substances possessing a high boiling point. This finding led to attempts to isolate the active principles involved.

It has since been found that if isoprene is exposed to a high temperature in an atmosphere of hydrogen, a mixture of compounds, chiefly aromatic in nature,
develops. This mixture was found to have marked carcino-
genic power.

Similarly carcinogenic substances were also pro-
duced by exposing acetylene and also yeast and human
skin to very high temperatures (Loeb, 53).

Numerous investigators during the past decade
have isolated pure substances from such mixtures and
indeed many of these have been synthesized.

Further chemical investigation has revealed a
basic similarity in structure between the molecules of
these various substances. It has been demonstrated that
it is the cyclo-penteno-phenanthrene nucleus which is
common to all these carcinogenic hydrocarbons (Evans,
25), and that a series of compounds related to 1:2
benzanthracene, which itself is inactive, possesses
especially marked carcinogenic properties (Loeb, 53).
The statement may therefore be made, in general, that
a molecular structure consisting of rings attached to
the 1:2 and 5:6 positions of the anthracene ring sys-
tem tends to confer a marked carcinogenic activity.

This series of investigations has revealed, there-
fore, that insofar as tar and the carcinogenic sub-
stances it contains are concerned in the etiology of
cancer, the action is much more specific than had
originally been supposed.

Their action according to Loeb (53) seems to be
directly as growth stimulating, as they apparently may induce cancer formation without first causing a local irritation. They are not selective as regards the tissue on which they act as they have been shown to produce tumors of connective tissue origin as well as of epithelial cells. They effect, step by step, changes in the cells on which they act, eventually resulting in the formation of cancer from originally normal cells.

Evans (25) called attention to the close similarity between the carcinogenic agents already described and cholesterol. Kennaway and Sampson (40) have obtained from cholesterol heated to about 800° C. products which caused epithelioma of the skin in mice.

Bourne (11) also commented on the close chemical similarity between the carcinogenic compounds present in tar and cholesterol --- even to the point of classing these substances with the sterols.

Such a structure he described also as relating them closely with the male sex hormone (androkynine); with the female sex hormones (theelin and theelol); with antirachitic vitamin D; and with the bile acids.
II. ESTROGENIC SUBSTANCES AND CANCER

Among the various agents described above as related to one another chemically it is of particular interest in the present discussion to study what similarities and what differences may exist between the carcinogenic agents in tar and the estrogenic hormone. In other words it is now in order to study what estrogenic effect may be produced by the carcinogenic agents of tar and what if any carcinogenic effect may be ascribed to estrogenic hormones.

Extensive investigations of these effects have been undertaken during the past twenty years. As a rule there has been found no relationship at all between carcinogenic and estrogenic potency. Some of the more potent carcinogenic agents display weak estrogenic power. Others display no estrogenic power at all. In this regard it is worthy of note that vitamin D is estrogenic while so closely related a substance as cholesterol is not.

It is especially interesting to note that Cramer and Horning (19) applied estrin in .01% chloroform twice weekly to the skin of mice in the same manner that earlier investigators applied tar and its constituent substances. In all of five males thus treated
carcinoma of the breast developed. The strain of mice used was one in which the females normally develop carcinoma mammae in large numbers, but in which the males never develop this type of tumor spontaneously. This demonstrated a specificity of estrin which is not possessed by the carcinogenic substances of tar --- probably arising from the physiologic specificity of estrin for the breast tissue.

Burrows (13) also reported carcinoma mammae occurring in two males of one hundred thirty ordinary mice treated twice weekly with ketohydroxy estrin in benzene. He believed this significant because of the rarity of spontaneous mammary cancer in male mice.

Schockaert (62) in 1935 described an ingenious experiment in which he treated three hundred mice with coal tar in the accepted fashion. To one subgroup he also gave dihydrofolliculin injections. In this subgroup tar tumors appeared four weeks earlier than they did in the controls; they were more numerous (65.2% as compared with 27.2% in the controls at the end of five and one-half months); and they grew more rapidly.

He interpreted this result on the basis of a predisposing and stimulating effect produced by the folliculin. His work has not as yet been corroborated, nor has it been contradicted.
Loeb concluded from his study of the facts as they are known and understood at present that:

"(1) there are substances which are both carcinogenic and estrogenic; (2) there are carcinogenic substances which are not estrogenic; (3) there are estrogenic substances which are not carcinogenic; (4) even in cases in which substances are both estrogenic and carcinogenic, there is no parallelism between the strength of these two activities."

III. MAMMARY CARCINOMA IN THE MOUSE

The discussion turns now to a very extensive series of experiments dealing with the significance of the ovarian hormones in the development of mammary cancer in mice.

In 1911 Lathrop and Loeb (46) described a family of mice in which the hereditary transmission of a tumor seemed to be apparent.

In 1914 (47) these same investigators described the results obtained from a series of experiments on the heredity of tumors in mice. This study was suggested from the common observation by breeders of mice that there was a tendency for carcinoma mammae in the mouse to occur in families. Their findings were, essentially, that there is a constant incidence of carcinoma mammae in pure strains
of mice, the incidence varying in different strains; that the age of development of the tumor tends to be constant in each strain, but varies in different strains; and that both these characteristics tend to recur in succeeding generations.

In a paper written by Slye in 1920 (64) she described the value of inbreeding of mice, not because it increases the incidence of cancer in mice (or in any other species), but because it emphasizes the hereditary makeup of the species or strain under study. Her work as well as that of many others interested in the same field has shown that, by inbreeding, strains of mice may be produced some of which show a high incidence of mammary cancer and some a very low incidence. The important fact is, however, that she is able to predict not only what percent of the females will show mammary carcinoma in a given strain, but also at what age period these tumors will begin to appear.

Given these basic facts as to the normal incidence of spontaneous breast cancer in mice the next step is merely to find what procedures other than altering the strain, will produce changes in this incidence.

**EFFECTS OF PREVENTION OF BREEDING:**

Lathrop and Loeb in 1914 (48) brought the attention of cancer research to the finding that in females
allowed to breed freely there was a considerably higher incidence of mammary cancer than in mice prevented from breeding. They also found that in non-breeders the age before onset of the tumor was greater than it was in breeders. These facts are entirely independent of the difference in tumor incidence in varying strains of mice, although they described the finding that in relatively poor breeders (where this was characteristic of the strain) the incidence of mammary carcinoma was also lower. The significance of this finding was recognized by the authors as of dubious nature.

Bashford in a communication to Lathrop and Loeb (48) stated that he found no influence of pregnancies on carcinoma in mice.

Lathrop and Loeb in 1916 (49) described further experiments which corroborated their previous results.

Maud Slye in 1920 (63) told of her experience with breeding females. She stated that without exception the amount of tumor grown while reproductive was much less than during her non-reproductive period, and that the amount of tumor grown by reproducing females was much less than that grown by non-reproducing females.

Leo Loeb again in 1919 (51) confirmed this finding that pregnancy decreases the rate of growth of adeno-
carcinoma of the mouse breast, but reported that breeding is associated with a higher incidence of mammary carcinoma. Some of his data is quoted in the table which follows. All of the mice used were of the same strain.

<table>
<thead>
<tr>
<th></th>
<th>Mice without tumors</th>
<th>Mice with tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-breeders</td>
<td>45 1/3%</td>
<td>54 2/3%</td>
</tr>
<tr>
<td>Breeders</td>
<td>32 2/3%</td>
<td>62 2/3%</td>
</tr>
</tbody>
</table>

W. S. Murray in 1927 (59) confirmed Loeb's claims and stated that enforced non-breeding delays very markedly the age of tumor appearance and may inhibit entirely development of carcinoma in mice which would probably have had a high tumor incidence had they lived a normal sexual life.

Cori (17) desired to check Loeb's work and found in 1927 that in his strain of mice, 94% of those females allowed to breed freely developed mammary cancer, while in non-breeding controls of the same strain only 78.5% developed tumors.

Thus there seems to be ample evidence to the effect that prevention of breeding in female mice (1) lowers the incidence of spontaneous mammary carcinoma and (2) raises the age before development of the tumor occurs. During reproduction, also, there seems to be a decrease in the rate of growth of the tumor.
EFFECTS OF REMOVAL OF THE OVARY:

To further carry out the studies on the relation between the ovary and the breast it seemed logical to attempt to find out what would occur in the absence of the ovary. Accordingly in 1916 Lathrop and Loeb (49) reported upon the results obtained by castration of female mice. They found that castration before the age of six months markedly decreased the incidence of spontaneous mammary cancer in these mice, and that when a tumor did develop it was at a later age. These effects were found to be greater than were the similar effects obtained by prevention of breeding. Castration after the age of six months was found to have little or no effect.

The authors claimed this to be the first experimental demonstration of internal secretion as an etiological factor in spontaneous development of cancer. They described this as a chemical factor superimposed on an hereditary factor distinct from itself.

In 1919 Loeb (51) re-described the work reported above with a large volume of discussion regarding theoretical explanations of his findings. This will be taken up further in subsequent discussion. He concluded that:

"In case such an influence of internal secretion should exist it must be a specific one. There is no reason to assume that removal of an organ with in-
ternal secretion should influence the development of cancer in organs the growth of which is not affected by their internal secretion under normal conditions".

Cori in 1927 (17) amplified Loeb's work by finding that in as high as 15% to 18% of castrated female mice there was a regeneration of the ovary. To eliminate the effect of this he followed his castrated mice by the use of vaginal smears to determine absence of ovarian function. In none of the females castrated before the age of twenty-two days where ovarian regeneration failed to occur did carcinoma develop. Furthermore the castrated mice lived on the average to a greater age than did either the non-breeding or breeding mice. Consequently in them there was a greater possibility for carcinoma to develop before they died.

Murray also in 1927 (59) compared the effects of castration and those of non-breeding. He found them to be very similar. He compared the age of onset of the tumors as follows:

<table>
<thead>
<tr>
<th></th>
<th>Youngest</th>
<th>Average</th>
<th>Oldest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breeding females</td>
<td>4 mo.</td>
<td>9 mo.</td>
<td>14 mo.</td>
</tr>
<tr>
<td>Non-breeding females</td>
<td>10 mo.</td>
<td>14.7 mo.</td>
<td>17 mo.</td>
</tr>
<tr>
<td>Castrated females</td>
<td>9 mo.</td>
<td>15.6 mo.</td>
<td>18.8 mo.</td>
</tr>
</tbody>
</table>

It may be concluded then that castration of the female mouse reduces markedly the incidence of spon-
taneous mammary carcinoma.

**EFFECTS OF OVARIAN TRANSPLANTS IN CASTRATED MALE MICE:**

The next step in the case against theelin was the attempt to produce mammary carcinoma in the male mouse—where such tumors usually are very rarely seen. This was carried out by the attempt to transplant ovaries from a female of the strain to be studied into a male, preferably a litter mate.

Loeb (51) began this type of work in 1919. In his series of mice there were no mammary tumors developed. However, he stated that many of the ovarian transplants failed to grow, and that many more were apparently never functional.

Murray in 1927 (59) transplanted ovaries into two hundred ten castrated male mice and in four of these tumors appeared by the age of ten to thirteen months. In two hundred forty-one castrated males of the same strain no tumors developed.

He reported in 1928 (60) that 7.1% of these male mice with the ovarian transplants developed tumors at an average age of 14.4 months.

Gardner (34) reported that he failed to find evidence of tumors in any of his series of male mice thus treated, although he described the development of the
male breast to an extent comparable with that in the normal virgin female.

EFFECTS OF THE INJECTION OF FOLLICULIN:

When Allen and Doisy in 1923 (3) isolated the active principle of the ovarian follicle they furnished the research workers with a new tool for investigating the relation of the ovary to mammary cancer. The investigations using ovarian follicular hormone are many, and only a few of the more important ones can be touched upon in the ensuing paragraphs.

Cori (17) as early as 1927 attempted to produce mammary tumors by injection of follicular hormone, but found that none were obtained. He felt that this was due to the fact that an oily preparation of the hormone was used and because of reactions to this the treatment could not be carried out over a sufficiently long period.

Lacassagne (42) obtained the first positive results in 1934 when he noted that in one family of mice treated by injections of folliculin there was more abundant and more precocious breast development than in another similarly treated. He found also that the former had a greater tendency toward the development of spontaneous mammary cancer than did the latter. There was also an apparent relationship between the estrus cycle and the cancer rate. This finding is part of another phase of the subject and will be considered later.
Harde (38) confirmed Lacassagne's work with somewhat less definite results. He also remarked that in mice belonging to strains displaying low tumor rates, the glands functioned less and the mothers nursed their young for a shorter time than did those mice belonging to high tumor rate strains where lactation was also greater. This interesting point brought out by Harde has not since been confirmed nor has it been discussed except in relation to the human.

Both Lacassagne and Harde remarked an exaggeration of estrus in mice during the precancerous state.

Lacassagne in 1936 (43) reported that in twelve males given weekly injections of folliculin from the time of birth, eleven developed adenocarcinoma of the breast. This he believed significant since males rarely develop this tumor. Seven of nine sisters of these males, all of whom were similarly treated, developed tumors pathologically indistinguishable from those in the males. In another strain where less than 2% of the females develop spontaneous mammary carcinoma five of six males and all of four females given similar injections developed mammary carcinoma. His series is quite small, but may be significant in view of the nearly 100% results.

Burrows (13) reported in 1936 because of the rarity of spontaneous carcinoma mammae in male mice the devel-
opment of such tumors in two males of one hundred thirty ordinary mice. These mice had been subjected to the application to the skin of a benzene solution of theelin.

Bonser reported in 1935 (9) and again in 1936 (10) that she had been studying the effect of weekly injections of ketohydroxyoestrin benzoate in two strains of mice. The males only were used. In three of nineteen males of a strain whose females show a high tumor rate, tumors developed. In none of thirty-four males of a strain of low tumor rate did tumors appear.

Suntzeff and co-workers in 1936 (68) stated that males are as prone as females to develop carcinoma of the breast if they are injected with large enough doses of estrin.

Cramer and Horning (19) reported that tumors appeared in all of five males subjected to application of oestrin in chloroform to the skin. This confirmed Burrows work.

Gardner and others (35) reported carcinoma in two of six males under weekly injections of keto-estrin benzoate.

MacDonald (56) in studying the effects of estrin and progestin in rabbits failed to find any evidence suggestive of a production of specific pathologic lesions of the mammary gland.
THEORETICAL DISCUSSION

Loeb (46, 47) early conceived the idea from his work that carcinoma of the breast was at least in part an hereditary condition. This conclusion was drawn from data which has already been described. He felt also that the hereditary factor was only a part of the etiology. He believed from his studies on the effects of non-breeding and of breeding in mice that there must be in addition to the hereditary predisposition an internal, intrinsic, or endogenous factor which affected the mammary gland. This he firmly believed to be the ovary. His idea was that in order for a carcinoma to develop in the breast there must be, first, an hereditary predisposition, and, second, an ovarian factor. This theory, of course, obviously explains the absence of such tumors in the males since only the hereditary factor was present in them. It also explains the varying tumor rates in pure strains, as he claimed that the tumor rate is either the product or the sum of the two factors.

He later altered his conception somewhat (51) to include as a third factor that of irritation, but he still held to the idea that neither the ovarian factor nor the hereditary factor alone can produce carcinoma. The absence of tumors in the male breast might result
from one of these things: (1) structural differences between the male and female breast; (2) absence of effect of pregnancy and/or nursing in the male; (3) absence of direct influence of the ovarian hormone. Of the three, he felt that the third is the more likely.

In 1924 the conception arose that the hereditary factor in mammary carcinoma might be identical with some inherited differences in the estrus cycle. Loeb adhered to his previous belief in two separate and distinct factors (52), but it remained until 1927 before he and Genther (54) studied and charted the estrus cycles of many mice of different strains. They found wide variations in the characteristics of the cycle in mice of the same strain as well as in those of other strains, and concluded that in all probability there is no definite relation between length of the sexual cycle (the ovarian factor) and the hereditary tendency to carcinoma. They added that work must, in the future, look further than the ovary to find the basis of heredity in cancer.

Bonser (8) in 1935 after similar studies concluded that there was no connection between the estrus cycle and what she designated as "a genetic factor" which "inhibits" tumor development. This is really a confirmation of Loeb's belief stated in a different manner.

Moskop, Burns, Suntzeff, and Loeb (58) in 1935 con-
firmed again the absence of correlation between the estrus cycle and heredity in mammary carcinoma. The same authors reported the same results again in 1936 (12, 67).

The only dissenting opinion is that of Lacassagne (42), who in 1934 claimed that he was able to demonstrate a relationship between breast development, cancer rates, and the estrus cycle. His work would indicate that precocious breast development and a high cancer rate were associated with a definite type of estrus cycle. This has not as yet been confirmed.

Cori (17) agreed with Loeb's point of view but added that the organ predisposition to cancer remains latent in the absence of ovarian function but becomes manifest when an amount of ovarian hormone corresponding to five to thirty estrus cycles has acted on the breast tissue. He felt, therefore, that the ovarian factor was really dual in nature -- first, it produced development of the breast, and, second, it provided a periodic stimulation of the breast tissue.

Murray (59, 60) suggested in 1927 and 1928 that one possibility might be that the cessation of ovarian activity after a period of activity was the chief factor in producing mammary cancer. Such a condition is found in female mice castrated later in life, and in
their case tumors developed more frequently than they
did in non-breeding females, where there was no cessa-
tion of ovarian activity. The accompanying table il-
lustrates this fact.

<table>
<thead>
<tr>
<th></th>
<th>Number used</th>
<th>% tumors</th>
<th>usual rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-breeding females</td>
<td>207</td>
<td>11.5%</td>
<td>80%</td>
</tr>
<tr>
<td>Castrated females</td>
<td>210</td>
<td>17.1%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Gardner (34) disagreed with Loeb and Cori. He
felt that the ovary was responsible for mammary carci-
noma only in so far as it developed the breast and
therby furnished a site in which the carcinoma might
develop. His contention was based on the finding that
in males treated either by ovarian transplants or by
estrin injections a duct system comparable to that in
normal virgin females developed. He was unable to ob-
tain tumors in any mice so treated, although all but
three were from susceptible strains.

If it be assumed, then, with Loeb, that for a
cancer to develop in the breast two factors at least
are essential -- namely, an inherited organ predispos-
tion and an ovarian factor -- the second of these
factors should be considered as to the mechanism
underlying its action. This has already been briefly
touched upon, but now the discussion turns to a more
careful consideration of this point.
Several mechanisms may be presupposed.

(1) According to Gardner (34) the ovarian hormone is a factor only in so far as it develops the breast.

(2) According to Allen (2) certain localized areas of mammary ducts may be more sensitive than others to stimulation with theelin. This was suggested by a finding already mentioned in the discussion of physiology.

(3) According to Lacassagne (44) carcinoma is most common in ducts commonly plugged (breast, sebaceous glands, sudorific glands, uterine glands, and the prostate) and the retained secretion may contain enough stagnant estrin to act as a carcinogenic agent. In favor of this view he called attention to the fact that colostrum is high in estrin content, and that, in the human, carcinoma frequently arises out of cystic disease of the breast.

Further evidence of this effect was given by Bogen (7) in 1935. By removal of young from the mother mice at birth there was a tendency for carcinoma to appear in those breasts which were not suckled. Similar results were obtained by ligating one nipple and permitting the opposite one to be suckled.
Suntzeff, Burns, Moskop, and Loeb (68) could demonstrate no effect on tumor production following ligation of the ducts, but the experiment was apparently not well controlled as secretions of the untouched breast were not removed by suckling.

Fekete and Green (27) performed a similar experiment save that they cauterized one nipple with a hot wire in place of ligating it. In a high tumor strain of mice they found that 55% of tumors which appeared following this procedure were in the breast whose nipple was obliterated. In a low tumor rate strain no tumors appeared in that breast.

A personal communication from Dr. J. H. Schmela regarding the incidence of carcinoma of the mammary gland in cattle is interesting. In his entire experience of twenty-five years as a veterinarian he has seen but two or three cases. The milk ducts of the dairy cow are certainly not allowed to become stagnated.

(4) According to Burrows (14) the effects of estrogens are limited entirely to organs belonging to or representative of embryologic remnants of the reproductive system. This indicates a specificity of theelin not possessed by other carcinogenic substances. Other authors described this same specificity (Loeb, 51; Cramer and
Horning, 19). Burrows in addition described the response to theelin obtained from such organs. Their epithelium undergoes apparently the following changes: (A) arrest of function, (B) hyperplasia, (C) metaplasia, and ultimate keratinization, and (D) suppuration.

Cramer and Horning (19) described the hyperplasia which occurs and labeled it the "precancerous condition".

All the theories so far advanced admit that the ovarian hormone is concerned in the development of carcinoma of the mammary gland of the mouse. The exact manner in which this takes place is still a matter for speculation and further investigation and cannot be determined at the present.
MAMMARY CARCINOMA IN THE HUMAN

EFFECTS OF BREEDING AND LACTATION ON TUMOR INCIDENCE:

As long ago as 1845 Sir Astley Cooper (16) said:

"Suckling ... diminishes the disposition to malignant diseases of the breast, for although women who have had children are still liable to cancerous and fungoid diseases, yet it is undoubtedly true, that breasts which have been unemployed in suckling, in women who have been married, but are childless, and in those who have remained single, are more prone to malignant diseases than those of women who have nursed large families ..."

Lane-Claypon (45) reported in 1926 a statistical study which was very elaborately worked out. This was a survey of cases in Glasgow and London hospitals. She stated:

"the married state and the production of children far from being conditions favourable to the occurrence of cancer of the breast, are substantially antagonistic to it. ... Lactation, even when repeated in successive pregnancies, does not appear, per se, to be a circumstance which has influence, one way or the other, on liability to cancer. ...The breast which has never been called upon for normal function is certainly more liable to become cancerous".
In her studies the women were divided into a cancer series and a control or non-cancer series. She found that in her control series as compared with her cancer series there were on the average (1) an earlier marriage, (2) an earlier climacteric, (3) a longer mean duration of marriage before the climacteric, and (4) more children and fewer miscarriages and stillbirths. The following chart displays these findings.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>CANCER SERIES</th>
<th>CONTROL SERIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at marriage</td>
<td>26.48</td>
<td>6.4</td>
</tr>
<tr>
<td>No. of children</td>
<td>3.48</td>
<td>2.88</td>
</tr>
<tr>
<td>Duration marriage</td>
<td>18.56</td>
<td>8.43</td>
</tr>
</tbody>
</table>

She found that those women who ultimately developed carcinoma bore 22% fewer children than the controls (allowing properly for the relative duration of marriage). This finding would indicate that fertility and low incidence of breast cancer are related.

She concluded also that any connection between cancer of the breast and lactation lies in the absence of function or in the excessive use of the breast. Unilateral lactation does not appear to have any untoward influence in causing cancer of the breast so used.

Von Winiwarter (77) in an extensive statistical study in 1878 concluded that the more seldom a woman gave birth to children the greater were her chances of developing mammary carcinoma.
While the studies described above were made from individual case records and therefore reflect an accurate picture of the cases studied, another method of analyzing large groups of cancer cases was undertaken in 1935 by Emil Bogen.

He (7) found from his studies of vital statistics that in those states with low birth rate (from females aged between fifteen and forty-four years at the time of their delivery) in the year 1900 there was a higher incidence of deaths from mammary cancer in 1930, among women over forty-five. The statistics were taken at this thirty year period to permit women in the childbearing years in 1900 to reach the cancer age in 1930. The inverse ratio he described above he found nearly consistent for all the states, and upon this fact he based his contention that breast cancer is more common in those states where the birth rate is low.

A study of vital statistics from countries other than the United States was made. This revealed a strikingly similar inverse ratio -- with England and Scotland high in death rates from breast cancer and very low in birth rate. Japan and Chile footed his list with low breast cancer death rates and high birth rates. However, in studying the material presented by Bogen too much reliance must not be placed upon data reported by
countries where registration of births and deaths is not well kept. Another fault lies in the fact that the average age at death is not constant in different countries and the possibility therefore exists that in some places the women develop cancer because they live longer.

However, his study is well worked out and is interesting from the speculative standpoint. Inasmuch as it supports previous studies it may be of value.

Thus, it has been found that comparative infertility or sterility is associated with a high incidence of breast cancer, and that among those women who have borne and nursed children the cancer rate is considerably lower.

**EFFECTS OF BREEDING AND LACTATION ON TUMOR GROWTH:**

It is important to distinguish between the effects of pregnancy and lactation on a tumor not yet present and on one already present and growing.

Trout (72) in 1922 described two cases of women, aged thirty-two and thirty-four years, each of whom had had amputation of one breast for carcinoma and both of whom subsequently became pregnant. About the sixth month tumors appeared in their remaining breast and grew unusually rapidly.

He reported also receiving letters from sixty-two surgeons. Of these, forty-six volunteered the informa-
tion that they had "noticed that pregnancy apparently stimulated cancer to develop more rapidly no matter where the growth might be located." In this series of replies were reported seventeen cases of breast cancer associated with pregnancy. All of these were seen late in the disease, and all went to a rapid and fatal termination. He also found in this series that there had been fifteen instances when pregnancy occurred after removal of one breast. Of these, thirteen (nearly 89%) developed carcinoma in the remaining breast and twelve died very promptly.

In 1934 Farati (26) described six cases of breast carcinoma in his clinic which were coincident with pregnancy or with lactation. He did not present details of these cases, but he concluded from his experience that the malignancy of breast cancer is markedly increased by either of these conditions.

In 1936 Schockaert (62) reported the cases of two females with mammary carcinoma who became pregnant. In both, the neoplasms grew unusually rapidly.

The frequency of carcinoma occurring in the second breast after amputation of the first has been investigated by Kilgore (41). In 1921 he stated that:

"the patient who has had one breast amputated for cancer is, if she survives five years, from three to
four times more likely to develop cancer in the second breast than a normal woman of the same age in either of her two breasts."

His description also told that he felt that the tumor appeared to be primary in each breast although in some cases it might have been metastatic. This he felt suggested a "cancer diathesis".

Emge (24) reviewed the literature pertaining to the effects of pregnancy on tumor growth. He found that an inhibitory effect on tumors in general was commonly described. However, he concluded that neoplastic tissue sensitive to hormonal stimuli may exhibit increased activity during pregnancy. He reported one case of breast carcinoma which had been previously treated by breast amputation and by X-ray. This patient developed a recurrence during a pregnancy. There was rapid metastasis, premature delivery, and death by the sixth month from a generalized carcinomatosis.

With this evidence it may be concluded then that in women who become pregnant after having had one breast removed for cancer, there is grave danger of it appearing in the other breast. This may be due to the fact that pregnancy seems to stimulate the growth of breast malignancies, and this effect may well be expected from the normal physiological stimulation of the breast during pregnancy.
EFFECTS OF OVARIECTOMY:

It is, of course, impossible to use ovariectomy in the human as an experimental means of studying cancer of the breast. However, in 1896, Beatson (5), an English surgeon, suggested on the basis of some observations which he had made that oöphorectomy might possibly be of benefit in treating a cancer of the breast. He used this method in two cases and reported the patients "cured".

Alexis Thomson (71) followed Beatson's ideas and analyzed eighty cases in which there had been used this sort of therapy. He found eighteen cases in which there was decided improvement and some regression of the tumors. Eleven cases showed less improvement, and fifty-one showed no appreciable change in the course of the disease.

CARCINOMA OF THE MALE BREAST:

It has been generally conceded that carcinoma of the male breast is a rare occurrence. Just how rare it is is shown by reference to the Mortality Statistics for the United States (75). Below is listed the number of deaths from cancer of the breast for several years' time.

<table>
<thead>
<tr>
<th>YEAR</th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Negro</td>
</tr>
<tr>
<td>1934</td>
<td>150</td>
<td>11</td>
</tr>
<tr>
<td>1933</td>
<td>145</td>
<td>21</td>
</tr>
<tr>
<td>1932</td>
<td>171</td>
<td>17</td>
</tr>
</tbody>
</table>
Obviously there is a marked difference in the incidence of this disease between the two sexes. Just what is the reason for this?

Of course the suggestion at once occurs to the investigator that the reason is the lack of breast development in the male. This, however, must remain speculative, as experimental studies on the human being are seldom permitted.

However, occasionally a male breast does develop. This condition is referred to as gynecomastia. The occurrence of this in itself is rare. When it does appear it is usually unilateral.

According to Geschickter, Lewis and Hartman (36) gynecomastia occurs most frequently in males of the white race between the ages of thirty and forty years. These men stated that the lesion is more frequently unilateral than bilateral, and in their series it occurred about just as frequently as carcinoma of the male breast. However in no case of gynecomastia did they find evidence of malignancy at any time.

Cheatle and Cutler (15) stated that the development of carcinoma in a breast which is the seat of gynecomastia has been recorded, but it is so rare that the event may be regarded as a coincidence rather than as an example of etiological relationship.
Thus although an occasional male breast does reach a "virginal" stage of development (so described by Geschickter, 36) the incidence of cancer in such breasts is low enough to eliminate the suspicion that the cause of the gynecomastia and the cause of the carcinoma of the breast are identical.

**ESTROGENIC HORMONE IN THE FEMALE:**

The following discussion deals with the occurrence of the estrogenic hormone in the human female.

Allen and Doisy (3) in a preliminary report on an ovarian hormone in 1923 described the isolation and partial purification of the ovarian follicular hormone. Thereby arose the search for its presence in other organs in the body and for its presence in excreta and secreta.

Before their discovery, Stockard and Papanicolaou (66) in 1927 described changes in the vaginal fluid of the guinea pig during various phases of its estrus cycle. Although they failed at the time to realize the value of this finding from the standpoint of its later use as a test for follicular hormone, such became the case. At present when follicular hormone is being tested for, virgin castrated female animals are used and the preparation being examined is injected. The vaginal fluid then reveals whether the fluid injected contained theelin or not, for theelin causes a disappearance of leucocytes
from the vaginal smear and produces a desquamation of keratinized cells in their place. Utilizing this method many interesting findings have been uncovered.

In 1930 Dingemanse, Freud, de Jongh, and Laqueur (20) were struck by their finding that in twenty-nine persons, all of whom had a carcinoma, very high quantities (up to 10,000 M. U. per liter) of menformon (follicular hormone) were found in the blood. They gave no details of the cases and drew no conclusions.

In 1932 Loewe, Raudenbusch, and Voss (55) told of Dingemanse's work and stated that Zondek in 1931 was unable to confirm this. They analyzed non-genital carcinomata of males and found 125 M. U. of female sex hormone per kilogram of tissue.

Frank (28) in 1934 described the normal content of female sex hormone in the blood. His figure was 1 M. U. per twenty cubic centimeters of blood. This he said is the maximum normal amount. In the urine there may be as high as 10,000 units per liter (as in pregnancy or during ovarian hyperfunction). He stated that he had found by this method that even after the menopause cyclical ovarian activity may continue for years. This is, of course, slightly diminished. In some cases it is, however, completely abolished.
He further described the normal findings in the blood and urine in 1934 (33) and in 1935 (29). The sex endocrine principles have been demonstrated in the placenta, in bile, sweat, saliva, and in cerebrospinal fluid. The estrogenic principle circulates each month in ever increasing concentration until the onset of menstruation when there is a marked drop. There is with this increasing secretion an increasing curve of urinary excretion.

During pregnancy a higher level of the estrogenic factor is noted in the blood after the eighth week, and there is a disproportionately greater increase in the quantities excreted in the urine.

After the menopause for as long as two years he has been able to demonstrate estrogenic factor both in the blood and in the urine.

Frank, Goldberger, Salmon, and Friedman (32) described the finding of large amounts of estrogenic factor varying from 800 to 8000 M. U. per kilogram in the psoas muscle of four normal cyclical females. On the basis of this finding they warned against basing conclusions on the mere presence of estrogenic factor in abnormal tissues unless it should later be shown (which as yet has not been done) that estrogenic factor is not widely distributed throughout the body of the human female.
In 1936 Frank, Goldberger, and Salmon (31) told of finding that the estrogentic factor continues to be excreted after surgical removal of the ovaries as well as after the physiological menopause. The same is found true after X-ray castration. No satisfactory explanation of the source of this estrogentic principle has been offered.
THEORETICAL DISCUSSION

In turning to a consideration of the relationship of breast cancer and theelin certain facts must be correlated. These are listed as briefly as possible in the following table.

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>EXPERIMENTAL ANIMAL</th>
<th>HUMAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breeding &amp; Lactation</td>
<td>Increases tumor incidence, Lowers tumor age</td>
<td>Decreases incidence</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Decreases tumor growth</td>
<td>Speeds growth</td>
</tr>
<tr>
<td>Ovariectomy</td>
<td>Decreases tumor incidence, Raises tumor age</td>
<td>promotes involution</td>
</tr>
<tr>
<td>Radiation castration</td>
<td>Decreases tumor incidence</td>
<td>promotes involution</td>
</tr>
<tr>
<td>Injection of folliculin</td>
<td>Produces CA in male or female of susceptible strains</td>
<td>Dangerous?</td>
</tr>
<tr>
<td>Incidence in males</td>
<td>Very rare</td>
<td>1 in about 100 cases</td>
</tr>
</tbody>
</table>

Any satisfactory explanation must, therefore, take into consideration the diametrically opposed findings in regard to the effects of breeding and lactation. This finding alone is so difficult to explain that it is sufficient cause for giving up any attempt at explanation on the basis of our present knowledge.

But this is not the only obstacle present. Other points which require explanation are: the rarity with which carcinoma appears in a male breast which is the seat of gynecomastia; the fact that in a considerable number of women cancer does not appear until many years
after the menopause; the fact that the bearing of children seems to exert a prophylactic effect against the development of cancer of the breast.

Certainly no one theory so far advanced can explain satisfactorily all these points. There have been already presented in connection with the discussion regarding tumor incidence in mice several theories.

The first of these considered the ovarian hormone a factor only in so far as it developed the breast. This is of course inconsistent with the observations in gynecomastia.

The second suggested that certain portions of breast tissue might be more susceptible than others to stimulation with theelin. This of course offers an explanation only for the pathogenesis.

The third of these was suggested by the frequency with which cancer occurs in glands whose ducts commonly become plugged. This stagnation theory has been taken up by several -- even in the pseudo-scientific manner of the lay press (Walter Martin in Coronet, 57). Lacassagne (44) hinted that estrin secreted into the ducts thus blocked might be the causative factor. He called attention in support of this suggestion to the high estrin content in colostrum. Others claimed other agents as the carcinogenic one. Bogen (7) suggested that reduced
derivatives of cholesterol (which were shown to be carcinogenic by Kennaway and Sampson, 40) formed in the stagnant secretions could be responsible. It is well known that milk contains a considerable quantity of cholesterol (Ansbacher and Supplee, 4). Lacassagne further called attention to the frequency with which cancer arises out of cystic disease of the breast. Geoffrey Bourne (11) called attention to the fact that there is a close relationship between the cancer age (which he designates as forty to sixty years) and the alteration in the sterol metabolism (evidenced by arteriosclerosis and other changes). He concluded, provisionally, that cancer research in the future will depend on research among the sterols.

The specificity of the carcinogenic power of theelin has been alluded to by many. This property should be expected from its physiological action upon the tissues related to the genital system.

Ahlbom (1) modified Wintz's views to say that even though theelin may have no direct carcinogenic effect, certainly its action in producing a periodic hyperemia and activity in the breasts during pregnancy and lactation and during the monthly cycle must be considered, at the very least, predisposing to the appearance of a cancer or distinctly dangerous to one already present.
PRACTICAL CONSIDERATIONS

In 1889 Schinzinger (61) propounded a theory upon which he hoped to base a treatment for carcinoma of the breast. This theory was developed following observations upon women who had for various reasons had bilateral oophorectomies. He noted the cessation of the menses, the withering and atrophy of the breasts. He knew the greater malignancy of carcinoma of the breast which develops during the child-bearing era. Thus his idea was to make the woman "old" while she was still young -- in other words remove her ovaries and precipitate an unusually early climacteric.

This plan of his he redescribed in 1905 (61) nine years after the British surgeon Beatson had suggested a similar idea. At that time he reported four cases in women between the ages of thirty and forty. In these cases there was rapid metastasis, recurrence, ulceration, and death despite a mammectomy. In several others past the menopause life was prolonged for many years after the mammectomy. He reported, however, no results from treatment following his plan.

Beatson in 1896 (5) suggested independently that women suffering from carcinoma of the breast be subjected to extirpation of their ovaries. His reasoning was
based on a different belief, however, as he felt that carcinoma of the breast was partly dependent upon an abnormal ovarian function. He reported two cases treated by castration as cured. They were undoubtedly at least alleviated.

In 1902 (5a) he described the indications for oophorectomy as requiring that the woman be still menstruating and that she have an absence of metastases in the viscera or bones.

He felt also that the thyroid had an action on the breast which antagonized that of the ovary. Consequently he also used thyroid gland extract ten grains, twice daily, in addition to the oophorectomy and the local treatment of the breast by amputation. No other investigators have confirmed his belief in thyroid, nor has it been used in this way since.

Alexis Thomson (71) was one of those to follow Beatson's lead. In 1902 he reported an analysis of cases treated by mammectomy and oophorectomy. In eighteen there was decided improvement, and life was prolonged for more than twelve months. In eleven cases there was decided improvement but life was not prolonged for twelve months. There were fifty-one cases with no appreciable change in the course of the disease. He concluded from his study that the beneficial results following oophorectomy are sufficiently established to eliminate any question of
coincidence or of error in diagnosis. He revised the indications for the procedure to say that (1) it is not contraindicated by the previous occurrence of the physiological menopause; (2) it is contraindicated by the presence of metastases in viscera or bones.

Lett (50) in 1905 reported an analysis of ninety-nine cases of carcinoma of the breast treated by oophorectomy in addition to local treatment. Of these, 23.2% showed very marked improvement; there was distinct improvement in thirteen others. If he omitted all cases over fifty years of age, seventy-five remained, and of these 29.3% showed very marked improvement; there was found distinct improvement in nine others. He obtained no "cures" with one possible exception. He noted that the improved condition lasted for a period which varied from one to five years.

Following these observations removal of the ovaries in breast carcinoma enjoyed a vogue for quite a period of time, but with the advent of X-ray and the discovery that it could be used to produce an artificial menopause and thereby obviate the dangers of a major operation, the popularity of surgical castration began to wane.

Foveau de Courmelles was apparently the first to use X-ray in castration for carcinoma of the breast. He began its use for this purpose in 1904 and from time to
time reported results. In 1926 (18) he discussed the question of dosage of X-ray necessary to produce cessation of ovarian function, and told that it varied with individual cases and that he himself varied it tentatively. He described none of the results obtained, but his technique included X-ray of the breasts and metastases as well as to the ovaries, and so the results were not well controlled.

Hugo Ahlbom (1) in 1930 described a series of one-hundred sixty-three cases treated in three different ways. Some received X-ray only to the ovaries, some to both the tumor, metastases, and the ovaries, and some only to the tumor and its metastases. From this controlled series he was unable to obtain statistical evidence of beneficial effect from the use of ovarian irradiation, unless he eliminated from his series all those women who were more or less debilitated before treatment was given.

As dosage, he used the following factors: a superficial dose of $\frac{2}{3}$ to 1 SED at focal distance 30 to 40 cm. with a filter consisting of .5 mm. of copper and 1 mm. of aluminium. This was given over two anterior fields each 12 x 12 cms. and one common back field 20 x 20 cms. The treatment was given in the course of three days. Current used was 6 mA., and the voltage was 160 kilovolts. By this means an active dose at least 40% SED was delivered to each ovary.
In 1933 Hoffman (39) reported a case in which there had been metastases in the scalp, chest and pelvis. By the use of heavy doses of X-ray to the pelvis (primarily directed at metastases there) he found that following the cessation of the menses the scalp metastases disappeared. The patient improved considerably and gained in weight and strength following this castration. Metastases present in the liver, however, apparently progressed.

The dosage he used he described as follows: 200 kilovolts, 4 mA., 50 cm. target-skin distance, given over four portals, 800 r units to each field. The time he gave as 75 minutes.

Taylor (69) discussed the general topic of "Artificial Menopause in Carcinoma of the Breast". He summarized in very good fashion the present day beliefs in regard to this subject very much as follows:

"Patients with inoperable and recurrent carcinoma of the breast may be benefitted by radiation castration. Younger patients may be expected to respond more favourably.

"Radiation castration following radical operation may inhibit or postpone the development of metastases.

"Subsequent pregnancy involves a grave hazard of recurrence of stimulating development of primary
carcinoma of the second breast and should not be permitted. In the cases who refuse radiation castration, simple mastectomy of the remaining breast should be considered.

"The treatment of operable carcinoma of the breast complicated by pregnancy should include prompt abortion."

With this last statement McGoogan is in almost complete accord. In a consideration of bone tumors complicated by pregnancy, yet unpublished, he will state that abortion is indicated in carcinoma of the breast where there are no bone metastases. He believes that abortion is of no value in saving the mother in such an event.

Witherspoon (78) in 1936 advanced the hypothesis that in patients with carcinoma of the breast whether it be primary or secondary, operable or inoperable, recurrent or metastatic, all ovarian activity should be destroyed by means of high voltage radiation by Roentgen ray.

Dresser (22) described his feelings in the matter, pointing out that carcinoma of the breast in a young woman is usually more malignant than in women who have passed the menopause; that it runs a more rapid course and ends fatally in a large percentage of cases regardless of all known therapeutic measures. He emphasized
the fact that pregnancy may cause an exacerbation of malignancy of the breast with an unusually rapid progress of the disease. He stated that an operable carcinoma is rarely observed late in pregnancy.

He reported a series of thirty pre-menopausal women with carcinoma treated by means of ovarian irradiation with remission of symptoms and regression of metastases in 30%.

On the basis of this he recommended routine examination of bones, lungs, etc. for metastases. If they are found absent he advised the procedure be radical mastectomy followed by ovarian irradiation if the woman is not past the menopause. If metastases are present he advised radiation to the breast, to the metastases, and to the ovaries.

Trout (72) in 1922 confirmed a belief that surgeons should warn their patients who are in the childbearing era and from whom a carcinoma of the breast has been removed, not to become pregnant for fear of serious trouble in the remaining breast.

Schockaert (62) sounded a similar warning note, adding that a woman suffering from or cured of carcinoma or any pre-cancerous lesion should never be given theelin for therapeutic purposes.

Steel (65) in 1936 described the results of X-ray
castration as follows: (1) disappearance of pain, (2) return to good health, (3) recalcification of bony lesions, (4) no relief from further or local radiation after recurrence, and (5) rapid death after recurrence.

He emphasized the value of X-ray castration in relieving the patient's symptoms for a variable time, and the rapid death of the patient which follows upon recurrence, he considered highly desirable as it relieved the prolonged bed-ridden stage of the untreated disease which causes so much grief to the patient, her family, and her doctor.

He reiterated the warning that further pregnancies should be avoided and that any woman under fifty who develops carcinoma should be immediately sterilized by the use of X-ray.

Dr. H. E. Hunt in a personal communication discussed the value of X-ray castration of the female suffering from breast cancer as a palliative means. He told of relief from pain and other distressing symptoms which is quite spectacular, following this treatment. He has had experience with it personally at the University Hospital and at Nebraska Methodist Hospital. The use of X-ray, however, is not limited to the ovaries in his technique, but is directed also against the metastases and the primary tumor if surgery has not been used. He told of a
feeling that irradiation castration has a definite place in the therapy of breast cancer.

He reported a personal communication from Dr. C. C. Little who has been working with irradiation castration of mice. He found that such treatment of females of strains with a high incidence of spontaneous mammary carcinoma markedly lowered this incidence. His work is as yet unpublished.

The therapeutic use of theelin in various gynecologic disorders has been frowned upon by editorials appearing in medical journals (23, 30). For that reason a discussion follows as to the dangers, if any, attendant upon its use.

Schockaert (62) in 1935 emphatically declared that theelin should never be given to a woman suffering from or cured of cancer or any pre-cancerous lesion. This of course on the basis of our present feeling in the matter does constitute a definite contraindication to the use of theelin.

E. C. Dodds (21) in 1935 was skeptical of the carcinogenic power ascribed to theelin. He felt that "an extensive search of the literature fails to reveal any incontrovertible evidence that the estrus-producing hormone is carcinogenic".
Hans Guggisberg (37) stated that while there is some evidence to show that some of the hormones underlie the development of certain kinds of tumors, the surface of this field has hardly yet been scratched.

Cramer and Horning (19) felt that theelin does exert a carcinogenic effect, but they called attention to the fact that in mice intensive therapy must be given for a long time in order to produce carcinoma. This period constitutes seven to ten years of a human life. He concluded that since no such active therapy as this is used in the human no alarm need be felt.

Nevertheless editorial comment warns against the use of large doses of estrogenic substances until further study establishes definitely their role. Estrin therapy should be withheld in patients with definite or possible susceptibility to tumors (23).

Frank, speaking editorially in the American Journal of Obstetrics and Gynecology (30) stated that the evidence of the estrogenic properties possessed by carcinogenic agents and the close resemblance chemically between these carcinogenic agents and the sex hormones is of extreme theoretical interest and no more.
SUMMARY

1 Because of recent warnings appearing in the literature against the therapeutic use of estrogenic substances and because of their similarity to carcinogenic substances found in tar, this subject has been investigated.

2 There is evidence that theelin is very similar chemically to pure substances isolated from coal tar and known to be carcinogenic.

3 Theelin, the follicular hormone, is responsible for proliferation of the ducts of the mammary gland, but requires the cooperation of progestin to produce alveolar proliferation.

4 It has been found possible to decrease the incidence of mammary carcinoma in mice by prevention of breeding or by surgical or X-ray castration. Breeding increases the incidence.

5 An opposite effect was found possible by the injection of theelin -- tumors appeared even in males thus treated.

6 In the human, pregnancy or lactation increase markedly the malignancy of breast cancer, and relative infertility or sterility is found to be associated with a higher incidence of breast cancers.

7 Oophorectomy has been used in treating breast can-
cers in women not yet at the menopause. At present X-ray castration is widely used.

8 Indications for X-ray castration are: (1) breast cancer in a woman not yet at the menopause, (2) operable or inoperable breast cancer.

9 Pregnancy is contraindicated by breast cancer, and if it occurs therapeutic abortion should be done, unless bony metastases are already present.

10 Women with breast cancer or any pre-cancerous lesion should not receive therapeutic injections of theelin or any of its related preparations.

11 There is no other contraindication to the use of theelin provided it is not given in massive doses nor over a prolonged period.
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