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CARCINOGENESIS OF THE SEX HORMONES

by

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I. INTRODUCTION

The therapeusis and etiology of cancer have been
unsolved problems in medicine since tumor growths
were first recognized. Many forms of treatment and
a similiar number of causative factors have been
postulated. These have evolved into a few known facts
and many more seemingly sound theories until at the
present time many who are interested in the subject
feel that in the near future the question mark of
cancer may be answered.

Because, in the past quarter century much experi-
mental work has been carried out in the field of cancer
research with surprisingly meager clinical results,
many readers of medical literature become skeptical
at the sight of original work in cancer. However,
at the present time, much can be learned from a review
of this literature. At present, certain etiological
theories may be set forth. It is probably true that
no one of these theories is correct in itself, but
rather a combination of factors are needed to give
carcinogenesis. A few of the theories set forth are:
(1) parasitic; (2) inception as a result of irritation,
usually chronic; (3) origin in nuclear aberrations;

(4) hereditary origin; (5) some perversion of metabolism; and (6) some hormonal imbalance. (Eggers, 1935) Equally true is the fact that no definitive treatment can be set forth until more is known of the etiology of the disease.

This paper is an attempt to review some of the more authoritative writers on one special subject in cancer--the sex hormones and their relationship to carcinoma. This is probably best studied from two points of view--the therapeutic and the etiologic association of the two sex hormones, estrogen and androgen, to carcinoma. On the whole, the works reviewed on estrogens are limited to carcinoma of the breast, while that of the androgens are limited to carcinoma of the prostate.

The paper itself will be made up of experimental work of the effect of the sex hormones on the various laboratory animals and clinical reports of the part that these hormones play in the etiology and treatment of carcinoma of the breast and prostate.

II. ESTROGENS AND CARCINOMA OF THE BREAST

A. General Considerations

That endocrines have been thought to have some
role in carcinogenesis has been shown by numerous
reports over the past half century.

The earliest report on the association of car-
cinoma of the breast to ovarian function is a note
by Schinzinger in 1889 that bilateral oophorectomy
may help in the treatment of carcinoma of the breast.
(Schinzinger, 1889) This was a mere observation,
but in 1896 a British surgeon presented the first
comprehensive article on the subject. He presented
two cases of carcinoma of the breast which seemed to
be helped by bilateral oophorectomy. He stated that
the result of these two isolated cases could not be
taken as conclusive evidence, but he presented the
cases in hope that further study in this field might
yield a helpful treatment for the disease. He con-
cluded: (1) that there seemed to be evidence that the
ovaries have some control in the body over local prolif-
eration of epithelium; (2) that the removal of the tubes
and ovaries have effect on the local proliferation of
epithelium which occurs in carcinoma of the mamma and
helps in the tendency cancer naturally has to fatty

degeneration; and (3) that this effect is best seen
in cases of carcinoma in young people, a class of
cases where local removal of the disease is often
unsatisfactory. (Beatson, 1896)

Beatson had several contemporaries who presented
cases which seemed to bear out his findings. Boyd
collected 54 cases of which 19 showed improvement,
(Boyd, 1900), Thomson reported 80 cases with 29 improve-
ments, (Thomson, 1902), and Lett presented 99 cases
and found improvement in 22. The last two groups were
all inoperable carcinoma of the breast. Lett also
observed that in those cases under 50 years of age,
the percentage of improvement rose to 41%. (Lett,
1905) Thus one sees that interest has been stimulated
in the subject being discussed for almost a half
century. Their conclusions varied--from 23 to 41%
improvement in cases of inoperable carcinoma being
treated by bilateral oophorectomy.

Interest in the above work gradually waned and was
forgotten until in recent years experimental work on
this subject has stimulated new enthusiasm in this
field. At the present time, one may review the work
of Beatson and his followers with some skepticism
because of their lack of knowledge of endocrinology
and their crude manner of observation as compared to

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the present exacting experimentation and accurate clinical observations; however one should not discount this first work that was done on the treatment of carcinoma of the breast. It helped to lay the foundation for present day experiments on the association of estrogenic action on carcinoma and is the basis for one school of thought on present day treatment of carcinoma of the breast.

After the above findings were presented at the turn of the century nothing further was written on the subject until the first experimental work on cancer in mice was reported in 1913 by Lathrop and Loeb. These workers showed that in cancer-susceptible-strains of mice the tumor incidence could be lowered and the average age of appearance raised by the prevention of breeding by castration. They added the following observations: (1) the incidence of spontaneous mammary cancer in mice--the species in which these investigations were carried out--varies greatly in different strains, (2) the hereditary cancer rate in successive generations remains constant, and (3) the cancer rate in breeding mice is higher than in non-breeding mice in almost all strains. (Lathrop and Loeb, 1913)

In the next few years much work was done in
respect to the effect of oophorectomy and its associa-
tion to cancer in mice. One of the more prolific
workers in this field was Loeb, who reported more
completely on his work begun in 1913. He demonstrated
that in strains of mice with high cancer incidence
the rate of mammary gland cancer could be reduced to
zero if the ovaries were extirpated at the time of
early sexual maturity (3-4 months); if oophorectomy
were carried out at 5-6 months the incidence was low-
ered but not to such a degree as if removed earlier
and the cancer would appear at a later date; and finally
if the procedure were carried out at still a later
date (8-9 months), the cancer rate rose still more
until in mice operated at 10 months the tumor incidence
was the same as in normal mice. One may conclude that
spontaneous mammary gland cancer in mice is due to
a combined group of actions: (1) factors transmitted
by heredity and (2) the growth promoting action of
estrogenic hormone. Thus given a constant hereditary
factor, the incidence of spontaneous mammary gland
cancer can be quantitatively graded in accordance
with the amount of estrogenic hormone given off by
the ovary during the sexual cycle. It seems that,

if a certain amount of estrogenic stimulation has accumulated in a tissue, some other cancerous agent elsewhere in the body is able to continue the work of the hormone, which a considerable time after the action of the hormone has ceased may evenuate in cancer. But without the estrogenic stimulation, the second agent cannot give cancerous transormation. (Loeb, 1916, 1920) All of Loeb's work has since been corroborated. (Cori, 1927) From the above experiments one sees that the significance of hormones in the origin of cancer has been proven by examining the effects of graded diminutions in their amount as compared with that normally active in high tumor strains. However, the effects of hormones on the development of tumors can also be shown by increasing it over the normal usually given by the ovaries.

In 1928 this new principle was introduced into cancer research when mammary cancer was produced in the male mouse. Male mice, even in susceptible strains, are usually free from mammary cancer; however, such tumors were produced by transplanting ovarian tissue into males. Murray reported the incidence of mammary tumors in the strain he was working with as follows; 80% in normal breeding females, 17% in ovariectomized

females, 11% in non-breeding females, and 7% in males
bearing ovarian grafts. (Murray, 1928)

Thus, up to 1928 one sees two general topics
under consideration in literature referable to the
carcinogenesis of the ovarian hormones. These are:
(1) clinical observations that bilateral oophorectomy
in some cases of inoperable carcinoma of the breast
is of some palliative aid and (2) experimental work
on carcinoma in mice of varying susceptibility strains
and the effect of oophorectomy on them.

It was not until 1929 that the crystalline ovarian
hormone was isolated. (Doisy et al, 1929) This
proved a boon to the cancer research worker and, as
Taylor states in his recent review of the pathology
of the ovarian hormone, two developments that made
possible the investigation of the pathology of the
ovarian hormone were: (1) attainment of potent prep-
arations of estrogenic substances and (2) elaboration
of methods of extraction and measurements of ovarian
hormone which can be applied to the study of its effects
on human tissues and body fluids. (Taylor, 1938)
Thus, after the isolation and production of estrogens,
it was possible to carry out more extensive experiments
on their effect in carcinogenesis. Two general

methods of study have been used. One is to take a given condition such as carcinoma of the breast, for which an endocrine basis is conceivable. Then evidence is sought to demonstrate hyperactivity of the ovary. The second method has been to begin with a known excess of estrogenic substance and attempt by its injection, usually into laboratory animals, to produce lesions similar to those in human beings.

B. Experimental Work on Estrogens

The pathological effects produced in animals by the administration of estrogenic substances include particularly the proliferation of glandular tissues of secondary organs of reproduction. The human lesions which may be analogous are certain hyperplastic and neoplastic conditions of the female and male genital tract. (Taylor, 1938)

Before one considers the experimental work on the estrogens in carcinogenesis, one should first look to other associated factors which are known to be present in order that mammary carcinoma may occur in mice. The first factor concerning this was the study of genetics of that disease. Pure strains of mice were developed by inbreeding. After a given number

of generations, the animals became chromosomally identical (homozygous) and the various physical traits could be expected to be reproduced regularly in their descendants. Through this method certain pure strains are established in which a large percentage of the females will develop breast carcinoma. Other strains have been bred which never or rarely develop neoplasms.

The anatomical structures in the breast of low-breast-cancer incidence mice show very slight development of acini on the duct system of the resting breast, while in that of the high incidence mice, myriad buds of epithelial cells are seen in the duct system. (Bittner, 1942)

The susceptibility of breast cancer in mice is hereditary, however Little proved clearly that it is not a simple Mendelian dominant but a more complex factor. It is transmitted by the maternal parent and does not follow the Mendelian law. (Little, 1931)

In general, the greater the hereditary tendency to mammary gland cancer, the more readily will the stimulation by certain quantities of hormone applied over a period of time lead to precancerous and cancerous changes. (Loeb, 1920)

In the case of cancer of the breast there is an

inverse ratio between the amount of stimulation and
the degree of hereditary factor needed.

Without the application of stimulating factors,
the transformation of normal into cancerous tissue
does not take place in the mammary gland, even if
the degree of hereditary tendency is very great.

Essentially, the hereditary factor in cancer
consists in an inherited degree of responsiveness
of mammary gland to stimulation. Therefore one would
expect that the different strains differ merely in
the amount of stimulation necessary. This is not
the case, for given a constant intensity of stimulation
applied in a unit of time, cancer will not appear
at the same age in the same strains. This indicates
that other variable factors complicate these relations,
but these factors are unknown. (Loeb, 1940)

Also in two different strains mammary cancer may
show very great differences in frequency, whereas
cancer of the cervix and vagina may be equally frequent
in both. The reverse condition may also be true.
(Loeb et al, 1936)

From this, one concludes that hereditary tendency
of cancer is an inherited organ peculiarity, corres-
ponding to the many other organ and tissue peculiarities

which a more thorough comparison of the life history
of individuals belonging to different strains reveals.

A second factor to consider in experimental
production of cancer in mice is diet. Bagg has shown
that it is necessary to supply high protein diets to
keep the animals breeding actively. (Bagg, 1936) Also
experiments have been carried out showing that under-
nourishment may be a factor (Tannenbaum, 1940) and
that the incidence of mammary tumors may be restricted
by caloric intake. (Visscher, 1942)

In 1933 a third factor was determined which was
instrumental in the production of mammary cancer in
mice. This was found to be an active principle present
during the entire lactation period in the milk of females
from strains with a high incidence of mammary tumors.
This may be eliminated by foster nursing on females
of strains with a low incidence of mammary tumors.
(Bittner, 1936) It was found that this principle was
especially active in the first 24 hours following
birth and during this time has much to do with the
incidence of cancer. In other words mice of mothers
with high incidence nursed the first 24 hours of life
by mice with low incidence of cancer show a decreased
incidence of the disease while the converse is also

true.   (Andervont, 1940)

A fourth factor and the one which is to be considered in this paper is the female sex hormone, estrogen. Soon after the isolation of the estrogenic hormone, experimental work was begun on the carcinogenesis of injections of this material into mice.

It might be noted before considering the effect of the estrogens that the sex hormones seem to be the only hormones with the exception of the pituitary that are important in carcinogenesis--at least as far as has been proven to date. Of course it is well known that the pituitary exerts a controlling effect over the sex glands.

It has been shown that spontaneous development of cancer in a high-incidence-cancer strain of mice can be prevented by the thyrotropic hormone of the anterior lobe of the pituitary gland, also the development of the mammary gland in males produced by prolonged estrinization can be kept in check by the simultaneous administration of thyrotropic hormone. Therefore the thyrotropic hormone is in some respects a physiological antagonist to the estrogenic hormone. (Cramer and Horning, 1938)

Transplants of the anterior pituitary into mice

caused a marked development of the mammary gland both
in strains with low and high incidence of mammary
cancer. They also caused a considerable increase in
cancer rate over that observed in virgin mice which
had not received such transplants. Mammary gland
cancer could not be induced, however, by this means
in very low tumor strains. In this respect transplanted
anterior lobes behaved like long-continued injections
of large doses of estrogen. (Loeb and Kirtz, 1939)

Many papers have been written on the association
of the other endocrines to carcinoma with rather
indecisive results. It is not the purpose of this
paper to discuss this questionable issue, but rather
to discuss the sex hormones which experimentally and
perhaps clinically have some association with cancer.

Lacassagne was the first to show the significance
of the estrogenic hormones in the development of
mammary tumors. He did this by injecting them in mice
over an extended period. He found he could produce
cancer in males of high-cancer-incidence strains.
In other words, no amount of treatment of males was
effective if they were of strains of which the females
normally would not develop breast cancer.

He carried out his experiments by weekly injections

of 0.03 milligrams of ketoestrin benzoate. All of
three male mice from a strain (R_3) in which 72% of
the untreated multiparous females showed spontaneous
development of mammary cancer gave rise to mammary
tumor. He then investigated the influence of estrogens
on the incidence of mammary tumors in male and female
mice from strains in which the multiparous females
showed few spontaneous mammary tumors. The initial
study indicated that the incidence of tumors in some
strains of mice could be increased greatly by injection
of estrogens. In one strain mammary cancer did not
develop. In the high tumor strain (R_3), 11 of 12
male and 7 of 9 female mice after estrogen was injected
presented mammary tumors. (Lacassagne, 1936) This
work has been confirmed by numerous other workers
with similar results.

Gardner and his associates injected four different
estrogenic chemicals (theelin, keto-estrin benzoate,
hydroxyestrin benzoate, and equilin benzoate) and
found that all were carcinogenic in mice.

In their experiments, which were similar to those
of Lacassagne, a total of 126 mice of three inbred
strains received estrogenic hormones for periods of
125 days or more. Twenty-eight mice have developed

one or more mammary carcinomas. The "CBA" strain is usually rather tumor-resistant, however, mammary tumors have occurred in two of three females. (Gardner et al, 1936)

Burns and Schenken have concluded likewise from similar experiments in which time was considered an important criterion. They injected a certain estrogen at regular intervals into male mice belonging to a high tumor strain. Injections for one month did not produce cancer; if continued for 2 or 3 months tumors appeared, but with diminished incidence as compared with that noted in breeding females. Injections over periods of 4 or 5 months yielded the maximum number of cancers; further increase in the length of time did not cause an additional increase in tumor incidence. (Burns and Schenken, 1940)

If the female sex hormone seems to be carcinogenic in certain strains of mice it seems plausible that the male sex hormone should prevent this action of estrogen under certain conditions. Experiments with this principle in mind were carried out. Testosterone was administered to female mice of a high-breast-cancer-incidence strain. This was successful if the male hormone was given early in the life of the animal;

but if given later in life, it had no effect in preventing cancer of the breast in mice. Thus it seems that after a certain period the animal has gained a certain "sensitivity" and the male sex hormones do not seem to control the cancer. (Nathanson and Andervont, 1939)

The significance of hormones in the origin of cancer has usually been proven by examining the effects of graded diminutions in their amounts as compared with that normally active in high-tumor strains. In addition to this method, the effect of the hormones can be demonstrated by increasing the amount over that given off by the ovaries under usual conditions. For this purpose ovaries from female mice of high-cancer, partly inbred strains were transplanted into castrated brothers. This method was the reverse of the one used previously and, although the first few experiments were negative, later more complete series were run in which cancer was produced in this way. (Loeb, 1940)

It must be remembered in evaluating the many experiments carried out on the relationship of estrogens to the various strains of mice that there are variations in these strains. The estrogenic stimulations seem to

vary in different inbred strains of mice. Some develop
few tumors. (Little et al, 1939) Others have a low
incidence in breeding females. (Bittner, 1939)
Andervont has shown some stocks to have a high incidence
in both virgins and breeding females. The greatest
variations in susceptible stocks have been observed
in "C_3H" strain having a very high incidence, and
virgin females of the "A" stock a very low one, whereas
breeding females of the two strains have a high incidence.
One wonders why this difference occurs in the incidence
in virgin females of the two strains. Andervont
explains it on a basis of (1) an increased production
of estrogenic hormone, (2) decrease in the rate of
distruction of these hormones, or (3) lower threshold
sensitivity of the mammary tissue to the neoplastic
changes. Therefore the amount of estrogenic hormones
produced in virgin females of various stocks is the
result of strain differences and as such may result
from intrinsic factors. In some susceptible strains
of mice the amount of hormones secreted by virgin
females will produce a sufficient development of the
mammary tissue to result in a high incidence of mammary
tumor. Other strains of susceptible mice have a low
incidence in virgin females probably because their

intrinsic factors are able to produce only a low level of estrogenic stimulation. The production of estrogenic hormones may be further increased as the result of extrinsic causes such as: (1) the production of young, as in the case of normal breeding; (2) forced breeding; or (3) injections of the hormone over long periods of time. Most of the experiments cited thus far use the last principle. (Andervont, 1941)

How do estrogens effect the mammary gland to produce mammary gland carcinoma in mice? Loeb has attempted to answer this question. He states that a sudden change does not occur from the resting gland or from the gland undergoing ordinary cyclic growth processes, either during the sexual cycle, pregnancy, or lactation. There is a slowly progressive stimulation of the mammary gland which may express itself either in mitotic proliferation, in secretion, or more generally in a combination of these two processes. Only very slowly do active growth and secretion processes set in. Preceded by intense growth and secretion processes which seem to be pre-cancerous, the carcinomatous transformation occurs. Abnormal glandular structures begin to develop which may protrude as papillae, or penetrate actively into surrounding stroma

and continue this growth even if the injection of estrogen is diminished. The end ducts and acini developing from them, rather than the individual cells, are the structural units of the mammary gland which are affected by these stimuli and which respond with growth and secretion processes. The estrogenic hormones thus produce cancer of the mammary gland by stimulating the gland tissue to greater and greater proliferation until the final threshold of normal growth is exceded. Thus the interpretation is that hormones produce cancer by stimulating epithelial structures in such a way that, step by step, the growth becomes intensified until cancerous transformation occurs. (Loeb, 1940) That these cancerous changes seem to be common to other genital organs has been substantiated by numerous workers. Gardner showed that abnormal proliferative changes were elicited in the cervix of mice by merely injecting estrogens subcutaneously. He proved further the cancerous nature of these proliferative changes by transplanting them successfully into other individuals of the same strain. (Gardner, 1938)

Loeb has made some very interesting observations on the administration of estrogens in mice. He concludes that estrogenic hormones produce cancerous

changes in mice in which the responsiveness to growth
stimuli on the part of the tissue (mammary gland) has
passed a certain limit. When this cancerous change
has occurred the estrogenic hormone is no longer
needed. Estrogenic hormones are effective because
they induce growth processes in the organs they help
to control, i. e. mammary gland, and estrogen does
not induce a refractory state to such a degree as some
of the hormones of a protein nature. If this were
true, the refractory state would inhibit the growth
stimulation. This refractory state in other hormones
may be due to the development of "immune substances"
which inactivate the hormone.

Furthermore, the hormones should not be cyclic
in their action. Many of the growth processes which
take place within the organism are cyclic. However
this does seem to be true of the ovarian hormones as
it is liberated rhythmically during the normal sexual
activity and during pregnancy. The tissue response
cannot be completely rhythmic, and the state of the
tissues at the end of the cycle is not the exact dupli-
cate of the beginning. This is easily observed by the
fact that even during the normal life of the female
mouse in certain strains, a slow but continued growth
of the mammary gland may take place with advancing age.

Apparently rhythmic growth processes may ultimately
lead to mammary gland cancer. Conversely, the mech-
anisms which tend to make growth processes strictly
cyclic, as well as those mechanisms which underlie
refractory states to the action of hormones, are
opposed to, and help to prevent the transformation of
normal into cancerous tissue. It may be assumed that
without these mechanisms spontaneous cancer would
develop more easily through estrogenic or any other
carcinogenic stimulation. Thus one sees a carcinogenic
agent (estrogens) being opposed by a mechanism which
in the normal organism tends to prevent abnormal
neoplastic growths. (Loeb, 1940)

C. Clinical Work on Estrogens

Most people believe that it is a long way from
cancer in mice to cancer in man. This is very true;
however, there are several important things one can
learn from studying the two.

First it must be said that there is no clear cut
evidence that estrogens are the etiological agent in
carcinoma of the breast in man.

On the other hand, since the etiology of cancer
has not been worked out definitely and often the
therapeusis is inadequate, one should attempt to

correlate the known facts in the experimental work just presented with the desireable knowledge of the etiology and treatment of carcinoma in man.

To apply these experiments clinically, one must make certain assumptions. First, the patients with cancer of the breast must be susceptible and must be secreting estrogenic hormone in increasing amounts. This increase should be comparable in degree to that used experimentally to produce cancer. Comparative susceptibility to cancer cannot be determined with certainty. As to the second assumption (that ovaries of these patients must be secreting estrogen in increasing amounts) no data has been published. Thus, one sees the problem of correlating experimental and clinical work. These assumptions have often been too enthusiastic, with the resulting skepticism in the clinical evaluation of the subject under discussion.

It is understandable if estrogens are a factor in human cancer there must be several degrees of relationship. Taylor places importance on this in order to study the pathological effects of estrogenic stimulation in the explanation of cancer. However he warns that theory is probably years ahead of any definite proof and all valuation of evidence must be guarded. He presents four classifications of the degree of rela-

tionship to cancer as follows:

1. The hormone may play simply a "protective" role maintaining the tissue in a state in which some other agent may be effective. This is the simplest explanation of why fibroids do not develop after bilateral oophorectomy.

2. The hormone may be effective only in starting the process, in causing a simple hyperplasia, while other agents are necessary to transform this to a tumor. A possible example of this is the development of carcinoma on the basis of endometrial hyperplasia.

3. The hormone may have certain indirect effects which by producing other types of stimulation lead to tumor formation. The stasis of secretions often noted in mammary ducts in which early cancer is present may be the result of a hormone and the cause of a chemical irritation.

4. Finally the hormone may be the true cause, but in two senses. It may represent simply a physiologic stimulus, which, when effective, excessively produces abnormal morphologic results; or it may be specifically tumor producing. (Taylor, 1938)

It seems reasonable that Taylor's theories of the varying degree of carcinogenesis of estrogens has a strong theoretical value, since the last word has not been said in regard to the etiology in man. Because much that is to be stated here is theoretical it is difficult to evaluate the evidence for an endocrine factor in human breast cancer. This can best be attacked from several different points and then a consideration of the relationship of these facts.

First, the age incidence has an important bearing on the etiologic theory. Approximately one-third of the cases of breast cancer occur in women with a mature menstrual function or premenopausal age group. Another one-third occurs within the 10 year period of unstable ovarian function or 5 years preceding and the 5 years succeeding the menopause. The last third are in the older age group past the menopause in which any develppment of cancer from the ovarian hormone must presumably depend on the continued development of abnormal cellular material having its inception many years before. (Taylor, 1938) However, Olch reports in his survey that about 50% of the instances of carcinoma of the breast are in women who first noticed a lump in the breast after they had reached 50. He does say that of these many have already passed through the menopause, and the remainder are still menstruating when they appear for medical attention. Further, it seems that estrogenic activity may be present in some women after the cessation of menstruation and this may be a factor in the development of mammary cancer at this late period. (Olch, 1937)

Taylor did some additional work on the disease in the younger age group and reports findings which seem to bear out the fact that the carcinoma is usually

more malignant in the younger women. This seems to
bear out the premise that if estrogens do have a part
to play in carcinoma, they would surely be most active
in the younger age group, thus producing the more
malignant lesion. He found that cancer of the breast
metastasizes earlier, it tends to be of higher grade
of malignancy, and post-operative recurrence takes
place more promptly in younger women. (Taylor, 1936)

A second point to consider along this same vein
is the time of menopause in women with carcinoma of
the breast. One must know this to evaluate the age of
onset of the disease. Again Olch has noted a delay
in the appearance of the menopause in these women.
This may indicate a physiologic state favorable to abnormal
epithelial proliferation. The age of menopause in
women normally is between 40 and 50--at least 72%
of women will be in this group while only 9-12% of
women will normally cease menstruating after 50. In a
series of 342 patients coming for carcinoma of the
breast first after the age of 50, the menopausal age of
55% was past 50. Thus almost 5 times as many women in
this group had a delayed menopausal age as is the
accepted normal. (Olch, 1937)

Even though statistics are often misleading it
seems that one can draw some conclusions. No matter

when the menopause occurs, there is some evidence that estrogenic activity continues after this and if it does not in other cases there is a distinct possibility that the carcinogenic action of the estrogens has affected the tissues prior to menopause. Although Taylor believes that the disease is quite evenly divided between premenopausal, postmenopausal women, and those women in the menopause, Olch has shown that there is a delayed onset of menopause in a high percentage of women with the disease.

Further in this discussion, it has been shown that young women with cancer of the breast often experience menstrual disturbances. This leads one to believe that there may be some hormonal imblance in women with cancer of the breast during their catamenia. (Lane-Claypon, 1936) Also lactation deficiencies occur with considerable frequency in the history of women with breast carcinoma. The significance of this is not clear but perhaps the failure to nurse is voluntary and the stasis of secretions produces irritation and finally cancer. Perhaps the failure to nurse is a physiologic deficiency based on some functional or structural abnormality, associated also with the cause of breast carcinoma. (Adair, 1934)

Strong evidence now exists that, just as in mice,

there is an hereditary factor in breast carcinoma.
It does not seem that this hereditary factor is equal
for all cancers. For example the familial incidence
of cancer of the breast is rather high while that of the
lip is low.

From this hereditary evidence one may get an
important insight into the difference between the
carcinogenesis of estrogens and that of the other
carcinogenic agents such as the hydrocarbons. Going
back to the experimental work already presented one can
see that production of mouse carcinoma by estrogens
is done with an environment which is entirely internal.
This is in direct contrast to the production of cancer
experimentally by hydrocarbons which is always done
externally. The existence of a carcinogenic environment
which is entirely internal enables one to understand
why malignancy can develop in organs not exposed to
influences from without. Therefore, the inference in
man which one may conclude from this familial incidence
is that carcinoma of the breast in women, at least in
those with a family history of breast cancer, is the
result of an internal carcinogenic environment. Since
in mice this internal environment is associated with
abnormalities in endocrine systems, a search for such
abnormalities in women with breast cancer and a family

history of the disease is indicated. (Cramer, 1937)

What evidence can be offered that will substantiate the known facts of endocrine carcinogenesis in experimental animals? Perhaps this is studied best by observation of already established breast cancer. First one may consider the widely held belief that breast cancer developing during pregnancy or lactation is of high malignancy and carries a grave prognosis. Secondly there is the effect of suppression of ovarian function by artificial means.

Pregnancy is the one physiological process which normally gives an increased amount of estrogen over an extended period. This is due to the fact that the corpus luteum is eliminated during pregnancy and the estrogenic secretion is maintained. From what has been said regarding the carcinogenic action of estrogens experimentally one would think that pregnancy in itself might be carcinogenic. This is just contrary to actual statistics for it is very uncommon to have cancer develop during pregnancy. Emge has reported that he has observed only one patient in 11,600 pregnancies with mammary carcinoma. This seems to indicate that pregnancy has very little association with the genesis of carcinoma of the breast and, as he shows, with

any genital tract cancer. (Emge, 1934) Peller substantiates these facts. He compared the expected number of neoplastic growths in pregnant and non-pregnant women estimated on the basis of known figures for carcinoma in various age groups. He found that actual occurrence of carcinoma of the breast in pregnancy was significantly lower than comparable non-pregnant groups of women. He concludes that the correlation between cancer and pregnancies in women is entirely different from that in mice. He even went so far as to say that pregnancy leaves the general body structure more resistant to the development of cancer, raises the average age of cancer occurrence, and retards its progress. (Peller, 1940)

It is well known that benign adenomas of the breast respond to the stimulus of pregnancy in the same ratio as does the normal mammary tissue. Such adenomas become more evident during lactation because of accumulated secretions. They usually recede after weaning but the process is repeated with each succeeding pregnancy.

Neoplastic growths are probably affected in a more complex manner. First it seems that they are responsive to general systemic influences of pregnancy.

This is expressed by cytologic changes just as normal
breast tissue and benign breast lesions are. Secondly,
these changes are not influenced beyond variations
in individual growth propensities. If these two factors
are in imbalance, the growth of the neoplasm will
be either increased or decreased in the pregnant over
the normal woman. Thus it is quite explainable why
much variance in opinions has resulted over the effect
of pregnancy on mammary carcinoma. Emge concludes
from the work presented above that pregnancy as a rule
does not influence the growth rate or the size of
neoplasms beyond certain reactions of which retard-
ation is the most frequent. In many instances it
remains unaffected and occasionally an acceleration
is observed. However he does state that neoplastic
tissue sensitive to hormonal stimuli may exhibit in-
creased activity during pregnancy. This seems to be
the case in mammary carcinoma. (Emge, 1934)

It is interesting to note the differences of
opinion which exist as to the effect of pregnancies
on carcinoma. There is much contradiction in the
literature and in some instances confusion. Taylor
is very emphatic about his views on the subject. He
states that pregnancy following radical mastectomy

for breast carcinoma involves a grave hazard of activating recurrence or stimulating development of primary carcinoma of the other breast. He concludes that treatment of operable carcinoma complicated by pregnancy should include prompt abortion. (Taylor, 1934)

Just as there is much difference of opinion as to the effect of pregnancy on carcinoma, so are there two schools of thought on its effect on the genesis of carcinoma. The report has been presented that most writers feel it has little to do with carcinogenesis. However others feel that the hyperfolliculinism of pregnancy favors the development of mammary carcinoma. Scapier exemplifies this school of thought and supports his belief by case reports. However he was undecided whether the cause of the mammary carcinoma could be attributed to the prolonged irritation of the mammary epithelium by folliculin or to a loss of hormonal equilibrium that accompanies the change from the stable condition of the nine months of pregnancy to the puerperal state. (Scapier, 1941) One sees now that the association of pregnancy and carcinoma has not been decided but must be studied more fully to warrant any conclusive facts.

The second bit of clinical evidence to support
the experimental work on mammary carcinoma is the
artificial suppression of ovarian function. The use
of the artificial menopause in the treatment of mammary
carcinoma is not a new thing. Beatson's work on this
subject in 1896 has been presented. One also has seen
how his work and that of his followers fell into disuse
after the turn of the century. This probably was
precipitated by the improvement in technique and
results obtained in radical mastectomy. However during
the past 15 years this original work has been revived
by many men and utilized with radical mastectomy in
the treatment of certain mammary carcinomas. The
method of gaining artifical menopause has been:
(1) surgical removal of the ovaries, (2) irradiation
of the ovaries, or (3) the administration of certain
androgenic hormones which seem to antagonize the female
sex hormones liberated by the ovaries.

Dresser was one of the first men to employ this
method of treatment in modern times. He reported
in his initial series from 1929 to 1934 fifty-nine
cases of carcinoma of the breast which received ovarian
irradiation. Thirty in this group had not reached
the menopause and nine or 30% of these have shown

definite regression of bone metastases as determined
by frequent roentgen examination. The regression is
manifest by destructive areas in the bone becoming
hyperplastic, and in some instances complete return
to normal appearance. There is concomitant relief
of pain and improvement in the general condition of
the patient. This may continue for a period of several
months up to two or three years. Thirteen of this
group (43%) were temporarily relieved of pain but
showed no regression of metastastic processes. In
eight cases (26%) there was no response. In the group
past the menopause, not a single case showed regression
by roentgenologic examination. The author concludes
that this method of treatment in the premenopausal
group is offered as a palliative measure and may be
expected to be effective in about one-third of the
cases treated. (Dresser, 1936)

Horsley made a study of cases of bilateral ooph-
erectomy with radical operation for carcinoma of the
breast. He has presented a comparison of this form
of treatment with that which he formerly employed,
that of radical mastectomy alone. Up to 1937 he
performed 184 radical operations with a 51% recurrence.
From November, 1937 to October, 1943 he performed

bilateral oophorectomy with the radical operation.
Of this series of 25 cases he has had only two (8%)
recurrences. One of these probably had internal
metastases at operation and the other patient had a
mucoid type carcinoma. Failure in the latter case is
probably due to the fact that pathogenesis of mucoid
carcinoma of the breast differs from that of the usual
mammary carcinoma. As it probably arises from the
stroma, estrogens do not seem to influence it. Nine-
teen of the 25 cases reported have gone from one to
six years after operation with one recurrence (5.3%).
This is quite significant in view of the earlier results
the author obtained by radical operation alone and is
probably more than an accident. (Horsley, 1944)
Even though these two series of cases vary as to the
time element and probably as to the extent of the
disease, it does seem that such a decided difference
in the results obtained points to the efficacy of
incorporating castration in the treatment.

Taylor, who has done much experimental cancer
research, has also employed castration in carcinoma
of the breast. He used artificial menopause following
radical mastectomy for operable carcinoma of the
breast. Forty-seven were studied with 14 patients

having no axillary node metastases. Of these, one
died of metastases and 13 are living and apparently
free from disease for an average period of 2.8 years.
Of the 33 with axillary involvement, 15 are dead, 3
are living with probable recurrence and 15 are living
without evidence of disease for a period of 2.7 years.
The author believes that this form of treatment may
be expected to result in temporary regression or
improvement in one-third of the cases with recurrent
and inoperable carcinoma of the breast. He obtained
best results in cases with osseous metastases. (Taylor,
1939) These results approximate those of Dresser
presented above.

From the cases presented one sees that castration
in breast carcinoma is of greatest value in controlling
to some degree the metastatic lesions. It helps to
diminish pain and other clinical symptoms and in some
cases of osseous metastases it seems to give roent-
genologic improvement. Hunt also gives a comprehensive
report on regression of pulmonary metastases following
irradiation of the ovaries in mammary carcinoma. He
presented two cases in which definite clinical and
roentgenologic improvement was observed following this
treatment. He believes the primary mechanism must have

been a biologic readjustment of the growth forces
following withdrawl of the stimulating ovarian hormones.
Other more potent and fundamental factors were involved
in initiation of the cancer. Growth of tissues may
be looked upon as influenced by two groups of opposing
forces. One promotes and drives growth; the other
retards and directs it. The ovarian hormones were
merely one factor promoting growth of the breast which
carried the tissue equilibrium more rapidly into the
cancerous phase. Withdrawl of the hormones resulted
in the reaction becoming reversed for a while but
other carcinogenic forces finally took over. (Hunt,
1940)

Taylor also states that best results of castration
are found in the younger patients and often postpones
or inhibits metastases in these patients. (Taylor, 1934)

It is well known that carcinoma in young women
is usually more malignant than those that have passed
the menopause. Lee has presented a review of 191
cases of breast carcinoma occurring in women under
40 years of age treated only by radical mastectomy.
A follow-up after three years showed only 15% alive
and free from the disease. (Lee, 1930) Taylor bears
out Lee's work in a report of carcinoma of the breast

at Massachusetts General Hospital from 1921 to 1929. The cases were divided into those patients from 46 to 60 years of age (postmenopausal) and those under 45 (premenopausal). It was found that carcinoma of the breast in the younger age group tended to metastasize earlier and was of higher malignancy than in the older group. Postoperative recurrence seemed to take place more promptly in the younger group. The treatment used was radical mastectomy and the results were 34% cures in the younger women as contrasted to 44% in the older group. (Taylor, 1938)

All this seems to indicate that, perhaps because mammary carcinoma is more malignant in the young, ovarian stimulation which would probably be more active in the young is one of the factors which gives carcinogenesis in man.

Another interesting fact is that, to date, no case of true carcinoma of the breast has been reported before puberty. This further adds to the increasing evidence incriminating the sex hormones since very little of this is active in man before puberty. (Power, 1942)

If estrogens in man seem to be carcinogenic, are there any specific case reports to substantiate this

premise? There are scattered reports throughout the literature which tend to incriminate the estrogens. These authors are very careful not to be too enthusiastic in their conclusions. Allaben and Owen presented a case in which 258,000 units of estrogen were given over a 12 months period for menopausal symptoms. The patient developed a breast malignancy subsequently and the medication was stopped. They suggest that, even though the estrogenic therapy might not be involved etiologically, the fact remains that it is a potentially dangerous drug and should not be given in unphysiologic quantities over long periods. (Allaben and Owens, 1939) Other cases have been reported with similar results and conclusions. (Auchincloss, Haagense, 1940; Parsons, 1941)

High incidence of breast carcinoma following the menopause is well known. In fact, as was shown, at least two-thirds of the cases are either during or following the menopause. If estrogenic activity is responsible for the genesis of the disease, how would one explain the high incidence following menopause? This has been adequately explained on several bases. Frank and his coworkers suggest that there may be an extra ovarian source of the estrogenic hormone. They have shown that 12 surgical castrates have excreted

some estrogens in the urine. This not only explains
the problem presented above but also may explain why in
certain cases of mammary carcinoma artifical menopause
does not seem to give the results that it does in
others. (Frank, et al, 1936) Robson and his associates
found estrogens in fairly large amounts in the urine
as late as 18 years after the menopause. There is
some evidence that this may come from other glands of
internal secretion, perhaps the adrenal. (Robson,
et al, 1934)

Another explanation seems to be that the estrogenic
hormone has "sensitized" the mammary tissue perhaps
over a period of several decades. Even if the meno-
pause intercedes, the tissue has reached a point where
some associated etiological factor may give rise to
the neoplasm.

It is known that ovulation usually stops after
the menopause. This eliminates the corpus luteum
which periodically interrupts estrogenic stimulation.
Ovarian conditions, especially if some cystic process
occurs, would lead one to expect a more or less con-
tinued estrogenic stimulation. This seems to favor
the premise that a hormonal imbalance may be an etiologic
factor in cancer of the breast. (Allen, 1940)

III. ANDROGENS AND CARCINOMA OF THE PROSTATE

A. General Considerations

Because there is a close analogy between the
female and male sex hormones in respect to carcino-
genesis, it seems fitting that reviews of the two should
be correlated. It is interesting to note the sim-
ilarity of the two subjects, their synthesis, discovery,
experimental and clinical application. This has lead
men interested in cancer to consider the two sex hormones
as having some association with its etiology and in
some cases the treatment of the disease of cancer of
certain genital organs.

It was reported as early as 1836 by two French-
men, d'Etoille and Civiale, that the testicular func-
tion had some control over the size of the prostate.
They mentioned that they observed complete disappear-
ance of the prostate in patients who had undergone
bilateral orchidectomy for treatment of double hernia.
(White, 1893) Of course any report on endocrine
function of that date is necessarily taken with much
reservation; however it does bring to light the fact
that a simple observation of over a century ago now
forms the basis of the most modern treatment for
certain cases of carcinoma of the prostate.

Although numerous reports are to be found throughout the nineteenth century similar to the above, not until 1893 did any truly scientific work appear. At that time White reported that castration of 35 dogs yielded atrophy of the glandular and muscular elements of the prostate. He suggested from this work that perhaps castration before a certain age in man might prevent the hypertrophy and subsequent carcinoma which often result in older males. (White, 1893) He then carried out castration on 111 patients with prostatic enlargement. From this study favorable clinical results were obtained. (White, 1895)

However, there were many conflicting reports on White's work. In 1896 it was reviewed and stated that, although castration was perhaps helpful, the best treatment for prostatic enlargement was prostatectomy. (Cabot, 1896)

Just as has been reported on the female sex hormone, after the turn of the century the work on the male sex hormone fell into obscurity. It was not until 1935 that discussion was once again started when it was stated that the female sex hormone acted as an antagonist to the male hormone and might prove a boon for the treatment of carcinoma of the prostate,

acting in an anologous role to orchidectomy. (Strohm, 1935)

Perhaps before the full scope of the work on carcinogenesis of the male androgens is considered, one should attempt to answer the question of why is the medical profession interested in cancer of the prostate? Most men realize the seriousness of carcinoma of the breast and the expedience of an early diagnosis but few realize that the same is true of carcinoma of the prostate. Statistics are often misleading but the ones quoted herein have been chosen since they seem to be a middle course between the extremely radical and the ultra-conservative. Approximately 45% of men over 40 have some benign hypertrophy of the prostate. Carcinoma of the prostate occurs in from 9 to 17% of all men over 50 while it is death-dealing in about 5% of all men over fifty. (Huggins, 1943)

The prostate is not known to produce a hormone and it is dependent for its existence in the adult upon two types of endocrines, the androgens and the estrogens. The androgens cause increase in size and the initiation and maintenance of the function of prostatic epithelium and in excess produce hyperplasia.

The estrogens in excess cause a decrease in size
and cessation of function of the epithelial cells.
Further, these fat soluble compounds have physiological
capacity of neutralizing the action of each other with
respect to the prostate when administered in appropriate
amounts. (Huggins, 1943)

B. Experimental Work on Androgens

One will note that the experimental work done
on the carcinogenesis of the male sex hormone is
much less prolific than that done on the female sex
hormone. This probably has its basis in two facts.
First, experimental work on carcinoma of the breast
and estrogens was started early (Lathrop and Loeb,
1913) and was found to be successfully carried out
in various laboratory animals such as mice, rats,
and guinea pigs. As none of the similar laboratory
animals have a true prostate, work on carcinoma of
the prostate and androgens was not started intensively
until this past decade. Secondly, because seemingly
good clinical results have been obtained in the treat-
ment of carcinoma of the prostate with the elimination
of the androgen, less work has been required to get
greater clinical results.

The gateway to androgen experimentation was opened
in 1927 when the male hormone was first isolated
from the sex glands of bulls. (McGee, 1927) In
1934 a Swiss chemist, Ruzicka, prepared it synthetically.
(Allen, 1939)

Following these two discoveries research on cancer
of the prostate took on a new role, just as research
on cancer of the breast did following the isolation
and synthesis of the female sex hormone. It became
a functional or physiological approach to the problem
of tumors rather than a descriptive or pathological
approach as was formerly done. The latter deals only
with sections of the dead organism while the former
deals with the entire living organism. To accomplish
this, one must know how much cancer activity is present
and how this can be increased or decreased. Assay
of the disease in the laboratory removes much of the
uncertainty of bedside observation. This is possible
in prostatic carcinoma through certain enzymes, the
phosphatases. (Huggins, 1943)

Kutscher and Wolbergs (1935) were first to find
that an enzyme capable of breaking down beta-glycero-
phosphate at an acid reaction (optimal pH 5) was
present in adult human prostate. It has been known

for some time that human serum contained a phosphatase
active on the alkaline side, but this was the first
acid phosphatase to be demonstrated. The alkaline
phosphatase is called into use during bone repair,
the enzyme being used to make available phosphate
deposition in bone structure as calcium phosphate.
(Rhodes, 1943) At the same time it was shown that
prostate tissue extracts split off inorganic phosphorus
from sodium nucleinate, a nuclease effect attributable
to nucleotidases, which are now classified as phos-
phatases. (Moore and Hanzel, 1936)

Gutman and Gutman have shown that infant's prostatic
tissue contained small amounts of this acid phosphatase
while in adults it increased in activity. Prostatic
phosphatase was found in primary prostatic carcinomas,
at the site of distant metastases, and in the blood
serum of patients with metastasizing carcinoma of
the prostate. These same men have carried out ex-
periments on monkeys and have shown that the adminis-
tration of testosterone (an androgen) increases the
amount of acid phosphatase while the administration
of estrogenic substances had little effect. (Gutman
and Gutman, 1938) Some have found rather unexpected
results from animal experiments in view of the results

obtained from human phosphatase levels. In sexually
mature animals, dogs were found to have 35.6 units/g
of phosphatase at a pH of 4.9, cats had 2.8 units/g,
rabbits had 1.9 units/g, guinea pigs had 3.9 units/g,
and rats had 2 units/g. Rat prostates, unlike other
animals contained considerable alkaline phosphatase,
15.5 to 54.8 units/g at a pH 9. (Gutman and Gutman,
1938) These animal experiments seem to bear out the
statement made above that, due to the fact no embryo-
logically homologous prostate is found in these animals,
it is difficult to use them in research of cancer of
the prostate.

However Huggins and Clark have done work on dogs
with normal and with hyperplastic prostates which is
well worth reviewing. They have observed that cystic
hyperplasia of the prostate occurs spontaneously in
senile dogs only when they possess physiologically
effective amounts of androgenic hormone. Both normal
and cystic prostates undergo marked atrophy when the
testes are removed, the chief difference being that
three months after orchidectomy there is a persistence
of slightly dilated clefts and spaces at the site of
the former cysts in the senile state.

In the castrated dog whose prostate is being

reconstructed as the result of the influence of daily
injections of androgens, certain doses of estrogens
prevent the increase of secretion and still larger
doses greatly depress the output of the gland.

In dogs with either normal or cystic prostate
glands the prostate decreases in size when estrogen
is injected in amounts to depress prostatic secretions
profoundly. The gland is maintained in an atrophic
state and overdosage avoided by controlled periodic
injections of stilbesterol until secretion is reduced
to the minimum, followed by free intervals, the estrogen
again being administered when secretion is measurably
increased. The shrinkage is related to depression
of male hormone production.

Overdoseage of estrogen causes the prostate of
dogs to enlarge and structures of the posterior lobe
and utriculus respond first with metaplasia caused
by this material. The prostatic enlargement does not
resemble the common cystic hyperplasia of the senile
dog. Metaplasia quickly disappears and the epithelial
structure quickly returns to normal when estrogen is
discontinued and androgen is administered. (Huggins
and Clark, 1938) This work seems to prove that the
prostatic secretions and the prostate are under the
direct control of the sex hormones.

Work on phosphatase levels in animals has been
quite discouraging as was shown by the result obtained
above. However monkeys do exhibit similar acid phos-
phatase activity to man and Rhesus monkeys were used
in the following experiments.

At a pH 4.9 it was found that there was marked
phosphatase activity of prostatic tissue. Unlike man,
adult monkey prostate tissue exhibits appreciable
phosphatase activity at pH 9 as in the rat. In the
prepubertal monkey both acid and alkaline phosphatase
activity of prostatic tissue are negligible. Following
treatment with testosterone, the phosphatase activity
of immature monkey prostates increased strikingly at
pH 4.9 and pH 9 to adult levels.

Within broad limits, the level of acid phosphatase
activity of prostatic tissue would appear to afford
some measure of the capacity to exercise some unknown
function of the prostate, which is deduced from the
extraordinarily high acid phosphatase activity in the
sexually mature man and monkey.

When estrogens were injected which acted chiefly
on the fibromuscular elements of the immature monkey
prostate, they did not evoke a significant rise in
acid phosphatase, whereas, a marked increase followed

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injection of testosterone which acts on glandular epithelium. (Gutman and Gutman, 1939)

C. Clinical Work on Androgens

Experimental work on any subject is of little value unless it can be correlated with clinical application in order that practical results may be obtained. Thus, even to a greater degree than the female sex hormones, has the knowledge of the male sex hormones been applied to the treatment of carcinoma and in particular, the prostatic carcinomas.

From the work presented it seems reasonable that acid phosphatase levels in the serum may be used as a guide to diagnosis and prognosis of cancer of the prostate. With this in mind and with no adequate treatment of the disease, many men in the past few years have accomplished good results by reducing the acid phosphatase levels through limitation of the male sex hormone. This may be done in any manner in which castration is effected, either surgical or artificial.

In order to evaluate the results from this method of treatment it is necessary to review selected case reports with their findings. The interesting thing

to note from this and following reports is the element
of conservativeness. Most men seem to be positive
of the definite aid this treatment affords, however,
they are reluctant to be too enthusiastic since all
of this work is of recent origin and must be borne
out by more complete reports of case studies.

Huggins was one of the first men to report on
the subject and his work seems to be held in high
esteem because of its authenticity and completeness.
He presents a series of 45 patients over a period
of 30 months with advanced prostatic carcinoma accompanied
by local infiltration or metastases. All were treated
by orchidectomy. Thirty-two of these patients had
metastases demonstrated on roentgenologic examination
of the bone. Twenty-one patients were operated upon
more than seven years before and 15 in that group had
osseous metastases.

Of the 45 patients, there have been 8 deaths,
all in men with extensive metastases to bone. From
a clinical standpoint, 31 men have had sustained improve-
ment lasting as long as 30 months; 9 men had temporary
improvement followed by recurrence of symptoms, and
in 5 there was no improvement following castration.

In 11 men of the 21 patients operated 12-30 months

ago there has been significant improvement; these patients are free from symptoms, acid and alkaline phosphatase values of serum are in or near normal range, there has been complete or partial resolution of roentgenographic evidence of osseous metastases, and a great decrease in size and in stony consistency of the primary neoplasm. Huggins classified the neoplasms into two groups, adenocarcinoma and undifferentiated carcinoma. All of the deaths, from carcinomatosis and the patients with slight or no improvement after orchidectomy, had undifferentiated carcinoma, while in the more satisfactory cases the cytologic appearance was adenocarcinoma. The findings of testes much lighter than the usual weight of 20 grams signified a poor prognosis.

In five cases of the series a great decrease occurred in the size of the primary neoplasm even though the metastases were advancing.

Estrogen administration was not found to be of value in the failure cases after orchidectomy. (Huggins, 1942)

Curtis has confirmed the work of Huggins with the presentation of similar case reports. He does bring up a few points which might be well to consider. He states that through the proper evaluation of

precastration and postcastration levels of serum acid
phosphatase the presence or absence, the regression or
extension of skeletal metastases may be adduced quite
accurately, although there is no correlation at present
between the height of these levels and the extent of
skeletal metastases present. Also, orchidectomy in
no way supplants other indicated surgical procedures
in the treatment of prostatic carcinoma, but should
be used in a majority of these cases to augment the
other treatment.

His results showed regression of metastases in
38% of the cases presented and in 14 of the 15 cases
the primary site of the neoplasm seemed to regress.
The symptomatic relief and clinical improvement co-
incides with Huggins' work. (Curtis, 1943)

Randall presents a series of 7 cases in which
orchidectomy was done from 7-9 years ago. His con-
clusions were rather indefinite but seem to be similar
to those already presented. He reported no cures
but in 3 of the cases clinical improvement was obtained.
However he was in doubt as to whether transuretheral
resection or castration was responsible for this. In
the light of the other works presented it seems rather
conclusive that only castration would account for the
improvement. (Randall, 1942)

Herger and Sauer have presented a very author-
itative report which further bears out Huggins' earlier
work. They carried out two treatments, surgical
orchidectomy and administration of stilbesterol, the
latter being used in cases where no metastases could
be found. In their series, which ran for 12 months,
diagnosis of cancer of the prostate was made by biopsy
in 85% of the cases. There was no evidence of metastases
in 57.3%; metastases suspected by clinical course in
6.1%; and definite metastases in 36.6%. It was found
by them that in administering stilbesterol it was
better to give small doses continuously rather than
large doses intermittantly. Their results follow:

	Stilbesterol	Orchidectomy	Both	Total	%
Died of disease	7	--	3	10	12.2
Died of other causes	2	--	2	4	4.9
Alive-- improved	13	3	10	26	31.7
Alive with progressive disease	11	--	4	15	18.3
No change	27	--	--	27	32.9
	60	3	19	82	100.0

(Herger and Sauer, 1943)

In evaluating the above table one sees that the per-

centage of patients aided (31.7%) seems to equal
Randall's but is only about one-half as encouraging
as Huggins' (31 cases with sustained clinical improve-
ment out of 45). Thus, there seems to be varying
results. This is to be expected and may be explained
by differences in treatment and observation.

Herger and Sauer in the above series also presented
very careful records of symptomatic relief obtained
which might be well to review. As to the size of the
primary site of the neoplasm they found regression and
softening of the lesion in approximately one-half of
the cases, no change in one-fourth, and an increase
in one-fourth of the cases. (Herger and Sauer, 1943)

It is of interest that although regression of
the primary lesion is reported in certain cases above,
from the microscopic standpoint no changes occur that
are characteristic of any modifications of the prostatic
cells with castration. (Herbst, 1942)

It was difficult for Herger and Sauer to evaluate
the effect of castration on urinary obstruction, how-
ever, in over one-half of the patients, no effect on
the degree of obstruction was noted.

Thirty patients had metastases. Ten of these
were treated with stilbesterol alone, 2 died of the
disease, one had no change, 4 were alive with pro-

gressive disease, and 3 were clinically improved.
Clinical improvement took place in 3 patients who had
orchidectomy alone. Of the 17 patients with both
treatments, 2 died of the disease, 3 died of other
causes, clinical improvement was observed in 9, and
evidence of further progression of the lesion was
observed in the 3 remaining cases. These figures seem
to indicate that castration is the most successful
treatment.

Pain from bone metastases was present in 22
patients. Treatment had no influence on the intensity
of pain in 5 cases and in 3 cases the pain became
progressively worse. The remaining patients responded
favorably. Nine patients showed complete disappearance
of pain but in 4 cases the improvement was temporary,
lasting from three to six months. Analysis of end
results indicate that lasting effects were obtained
only in a limited number of patients.

It is difficult to evaluate the effect of treat-
ment on bone metastases since x-rays taken at different
times are not alike. However only 3 of 23 patients
followed showed any evidence of regression of bony
metastases roentgenologically. (Herger and Sauer,
1943)

How does serum phosphatase play a role for the

clinician in carcinoma of the prostate? The role that
it plays in experimental work on carcinoma of the
prostate has already been described. Clinically,
phosphatase measurements are used to simulate the
measurement of the prostatic secretions as was carried
out in dogs. By the above statements the analogy is
explained. To prove this, three ptients with extensive
bone metastases from prostatic carcinoma were given
testosterone. A prompt rise in serum acid phosphatase
occurred in all and it seemed clear that the disease
was made worse by making the amount of available and-
rogenic material increased. Conversely, when these
patients were castrated (decrease in amount of androgens),
the acid phosphatase dropped and the alkaline phosphatase
increased as an index of an increased rate of bone
repair invaded by the metastasizing tumor. This effect
was so striking that it seemed safe to conclude that
castration resulted in a decrease in activity of
prostatic tissue. (Rhodes, 1943)

Thus one sees that through actual clinical application
measurement of acid and alkaline phosphatase is a
criterion to the extent of prostatic carcinoma. How-
ever the elevated phosphatase levels in cancer of the pros-
tate are due to two different mechanisms. Elevation of the
acid phosphatase is due to the prostatic epithelium and

and is directly associated with a malignancy of that organ while elevation of alkaline phosphatase is due to osteoblasts. It is associated with prostatic cancer in so far as there is an increased osteoblastic function as a result of invasion of bone by tumor. (Huggins and Hodges, 1941)

Dean and his coworkers have recently reported a comprehensive study on the phosphatase levels in a series of cases. They show that 19 of 26 patients showed elevated acid phosphatase before treated by castration while 7 had normal phosphatase levels. In 16 of the 19 with high levels, the quantity diminished during the two months following castration. They also confirm Huggins and Hodges' report that when the disease has invaded bone, its activity is reflected in the degree of elevation of acid phosphatase in the blood. The activity of the bone defense is indicated by the amount of alkaline phosphatase in the blood.

After castration, the activity of the prostatic carcinoma in bones probably decreases as is shown by the drop in acid phosphatase. They state that one would expect the alkaline phosphatase, an index of the attempt at bone repair, would also decrease as need for repair becomes less urgent. This does not occur in the majority of cases and may be explained possibly

by the fact that the shift in hormone balance following castration may stimulate the regenerative capacity of bone. (Dean et al, 1943)

Herger and Sauer have carried out phosphatase studies with similar results. However their figures do show that many of their patients with carcinoma of the prostate with no bone metastases show acid phosphatase levels well within normal limits. They conclude that acid phosphatase determinations are probably most helpful diagnostic aid in the early recognition of bone metastases in new patients and in determining the prognosis in patients under observation. (Herger and Sauer, 1943)

IV. SUMMARY AND CONCLUSIONS

Castration as a method of treatment for neoplasms of the prostate and breast was first used in the last decade of the nineteenth century. Following the turn of the century popularity of this treatment declined and was supplanted by more radical operations of the primary lesion.

It remained for modern experimental endocrinology to revive castration as an accepted treatment for carcinoma of the breast and prostate.

A. The Estrogens

This experimental work resolved itself into several different phases. The research on breast carcinoma was begun early (1913) and was carried out in the most part on mice. Inbreeding was done to determine hereditary factors. Castration, transplanting ovarian tissue to males, and the injection of the ovarian hormone into various strains of mice were used to determine the control that sex hormones had over breast cancer. Mice with certain hereditary tendencies were foster nursed by mice of other tendencies. The control of the pituitary over the ovaries was studied.

Out of these experiments came the knowledge now possessed about carcinogenesis of estrogens in mice.

This includes: (1) mice must have certain hereditary tendencies in order that estrogens may stimulate carcinoma, (2) estrogens seem to "sensitize" the mammary tissue so that after a certain amount of stimulation, cancer will result even if the estrogens are removed, and (3) several factors besides heredity and estrogens may be involved in carcinogensis. These include nursing, diet, and several unknown factors. It has been demonstrated that the greater the amount of one factor present, the less is required of a second factor to produce carcinoma.

All the experimental work presented is quite conclusive in proving estrogens are carcinogenic in mice. However what I was interested in in writing this paper was the evaluation of sex hormones and carcinogenesis in man. After reviewing the literature I do not believe that there is enough clear cut evidence to say estrogen is the etiologic agent of breast carcinoma. There is justification in pointing out experimental and clinical investigations that are similar and that seem in some degree to prove the question raised.

Susceptibility can definitely be shown in mice however it is practically impossible to show this in man. This subject should be given further study.

Estrogens may be controlled at will in mice.
They may be increased over the normal by injection or
eliminated completely by castration. Control of
estrogens in man is difficult and it is impossible to
say that the ovaries of one patient are producing more
or less female sex hormone than those of another.
However this problem has been attacked by various means
in man to prove that similar conditions exist to those
produced in experiments. First, scattered reports
have been presented to show with rather inconclusive
results that incidental strenuous estrogenic therapy
has produced carcinoma. Secondly, pregnancy, at which
time large amounts of estrogen are known to be present,
has been incriminated by some and exonerated by others
as being a stimulus to carcinoma. Lastly, and with
the most conclusive evidence, the results of castration
in the treatment of breast carcinoma have been presented.
We must depend on this to give the best support to the
theory that estrogens are carcinogenic.

This treatment seems to arrest the disease for a
time and is more helpful in treating the premenopausal
than the postmenopausal case. This seems to incriminate
the estrogens since it is known that more estrogen is
present in the pre- than in the postmenopausal woman.
It is interesting to note that estrogens have been

discussed in the light of being carcinogenic. Carcino-
genesis is difficult to prove but I believe that
castration treatment in itself proves the fact that
the estrogens are carcinomatous agents in so far as
they promote new growth after it has been established.
I believe the transitory effect of the treatment in
some cases is due to other carcinomatous agents inter-
ceding after the estrogens are eliminated.

No prepubertal cases of breast carcinoma have
been reported. This means that in the phase of life
when no estrogens are present, no neoplasms occur.

How is the fact explained that most carcinoma of
the breast occurs after 50 and also why is it that
castration sometimes fails in giving improvement?
The breast tissue of some probably requires long stim-
ulation from the carcinogenic agent and even if this
agent (estrogen) is eliminated at the menopause,
enough stimulation perhaps has preceeded to prepare
a fertile field for some other agent to intercede
and give the neoplasm at a later date. Also the
proof has been presented showing that in some instances
postmenopausal and even surgical castrates still
produce estrogen. This helps to explain why the
disease may appear after the menopause and why castra-
tion fails as a treatment in certain cases.

B. The Androgens

I found the experimental work on carcinoma of
the prostate much less prolific than that of the
breast. This was mostly confined to the effect of
androgens and the phosphatases. The levels of these
substances in serum have been found to be controlled
by the injection of estrogens and androgens in the
monkey. Also, no cystic hyperplasia of the prostate
was found in dogs unless a high level of androgen was
present.

With these facts in mind phosphatase levels were
determined in man. Before puberty low levels of acid
phosphatase were found. Following puberty normal
levels appeared and when prostatic carcinoma developed,
very high levels were encountered. This has been
utilized in the treatment of the disease for castration
eliminates the androgen and consequently the high
acid phosphatase levels. Very good clinical results
have been obtained and it also has been found that
phosphatase levels may help to give the diagnosis and
prognosis of the prostatic carcinoma.

High acid phosphatase levels indicate increased
activity of prostatic epithelium and perhaps a neo-
plasm of that organ. Alkaline phosphatase levels measure
the osteoblastic reaction and is associated with the

malignancy in so far as there is an increase of these cells as a result of osseous metastases.

I have attempted to review all of the pertinent literature on the sex hormones as associated with carcinoma. From this study I believe that one might conclude:

1. The sex hormones have not definitely been proved to be carcinogenic in man.

2. The female sex hormone under some conditions is carcinogenic in mice.

3. Certain human reactions agree with experimental work on female sex hormones while others disagree.

4. Oophorectomy as a treatment for carcinoma of the breast is helpful in selected cases.

5. The sex hormones seem to control the activity of the prostate in monkey and man.

6. Phosphatase levels are an accurate guide to the activity of the prostate.

7. Diagnosis and prognosis of prostatic carcinoma can be aided by observation of phosphatase levels.

8. Orchidectomy as a treatment for carcinoma of the prostate is helpful in selected cases.

9. If the sex hormones are carcinogenic in man, other associated factors must be present to give carcinoma.

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