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INVESTIGATIONS ON THE RELATIONSHIP OF OESTROGENS, CASTRATION AND CARCINOGENESIS

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Much attention had for long been devoted in the literature to the question whether oestrogens are carcinogenic in general, and carcinogenic to the female genitals in particular. Lately, the relationship of oestrogens and carcinogenesis has become a problem of intensified interest, due largely to the recognition of the chemical affinity between oestrogenic substances and the carcinogenic carbohydrates, and of the stimulating effect oestrogens exert on cell growth.

In animals, primarily in rodents, the carcinogenicity of oestrogens is to-day an accepted fact. LATHROP and LOEB (1916) were the first to study it, and LACASSAGNE (1939) and, chiefly, LIPSCHUTZ (1950) have proved it. Incidentally, considerable evidence has come to light in favour of an important role of the follicle hormone not only in epithelial but also in fibroid tumours. For instance, PYBUS and MILLER (1938) demonstrated that in mice 67 per cent of the cases of osteosarcoma are encountered in females. Another example is that on oestrogenic treatment the incidence of spontaneous lymphoid tumours in mice increases from the average 2 or 3 to 15 per cent.

Despite fair uniformity of results in animal experiments, the problem had for a long time remained confined to the laboratory, because no clinical observations were coming forth to show that these results held good for human subjects, and clinicians on this ground persistently refused to admit any carcinogenic significance of the follicle-hormone. This situation has substantially changed in the last 10 years ; moreover, the problem has developed into one of the highest importance in gynaecological oncology. The great number of studies shows the existence of two camps ; one is in favour of, the other definitely denies, relationship of oestrogens and carcinogenesis.

The majority of the papers on the subject has been devoted to markedly oestrogen-producing tumours, or to lesions due to excessive or protracted oestrogenic effect, in combination with cancer (TAYLOR, 1932 ; NOVAK and YUI, 1936 ; SPEERT, 1949 ; INGRAM and NOVAK 1951 ; GUSBERG, MOORE and MARTIN, 1954 ; and others). The rest reports on cancer induced by means of oestrogenic substances (FREMONT—SMITH et al., 1946 ; VAS, 1949 ; NOVAK, 1951 ; WALZ, 1952 ; SCHÜLLER, 1954 ; and others).

Clinical research work began with TAYLOR's (1932) histological study of 128 cases of uterine cancer. In 11 of them, there was a non-cancerous endometrium along with the cancerous tissue. In 9 of these 11 cases, the non-cancerous endometrium showed cystic glandular hyperplasia, an endometrial lesion which, chiefly from the work of SCHRÖDER (1934) and SZARKA (1934), is known to be due to excessive or protracted oestrogenic effect. TAYLOR's findings were confirmed by NOVAK and YUI (1936), who in the presence of adenocarcinoma demonstrated regularly hyperplastic areas in the endometrium in 24,3 per cent of their cases of corpus cancer. Years had to pass before gynaecologysts again took up the study of this problem. Renewed attention was directed to it by DOCKERTY (1940), when among 38 patients of the Mayo Clinic, affected with granulosa-cell tumour of marked folliculine production, he found 8 cases of cancer of the body of the uterus and 3 of breast carcinoma. Intensified research work has followed his report and still yields publications to some of which we propose to revert later in this paper.

In the relationship of oestrogens to carcinogenesis we began to be interested in 1945, and so were among the first to grapple with the problem from a clinical angle. Unlike TAYLOR, NOVAK, and DOCKERTY, respectively, for our point of departure we took a syndrome frequent in gynaecology, namely, cystic glandular hyperplasia of the endometrium in combination with cancer. Apart from being much more often encountered than endometrial adenocarcinoma and oestrogen-producing uterine tumours, the lesions hitherto used in this kind of study, our selected syndrome, being itself the result of a lasting oestrogenic effect, was expected to yield more readily evaluable data by which to disclose a possible relation of oestrogens to cancer of the body of the uterus.

In 1945, at the 1st Department of Gynaecology, among 211 cases of hyperplasia 4, or 1,9 per cent, and in 1946, at the 2nd Department, of 364 cases 8, or 2,1 per cent, were found to display corporeal adenocarcinoma. Thus, in two independent groups nearly the same incidence was revealed for the occurrence of the combination. Since cancer of the body of the uterus most frequently occurs in the menopause and since in our two materials the cases of hyperplasia combined with carcinoma also were of menopausal age, we were careful to include only such hyperplasias into our considerations as were known to have originated in the climacteric ; and it is only their number to which the number of carcinomas is referred. Are values to be obtained which lend themselves to evaluation, the comparison is to be one between the incidence of hyperplasia associated with cancer of the body of the uterus and the average incidence of the latter alone. This appears to be the only way in which to establish whether corporeal cancer in combination with a lasting folliculine effect is appreciably more or less frequent than cancer of he body in itself. At the time of our investigations there were no statistics available (and concerning that subject, none are available to-day) on the incidence of cancer in individual age groups and at the same time

of the various gynaecological locations. There were only the statistics of MELLY (1928) on which to fall back. According to his findings, 3,4 to 3,6 of every 10 000 women are affected with uterine cancer (0,036 per cent). Obviously, the difference between MELLY's statistics and the incidence of a combination of hyperplasia and corporeal cancer as found in our two independent groups, is far too great to allow of explaining the relative identity of these two ratios on the basis of chance alone. This view seems to be confirmed in the light of cancer checking in the near past in the Soviet Union (KRAVTCHENKO, 1947 ; LURIE, 1947 ; SHORDANIA, 1949 ; SIROVATKO, 1949), where 3 to 4 out of every 1000 women above 35 years of age, and recently in Budapest, where 84 of 19 500 checked women past 35, were found to suffer from uterine carcinoma. In view of the generally known fact that approximately 10 per cent of the uterine carcinomas are cancers of the body of the uterus, the average incidence of the latter can be taken to be 0,03 per cent. The great difference between this rate and the 2,1 per cent rate found by us for endometrial hyperplasia associated with corporeal carcinoma makes it clear that the latter was not merely an incidental finding. In relation to this great difference the error inherent in our having compared slightly heterogeneous statistical data is certainly negligible.

These findings seem to be in keeping with our previously made assumption that there must exist some kind of relationship of oestrogens hyperplasia, and cancer of the body of the uterus. It should be remembered, however, that we have never conceived of hyperplasia as a carcinogenic factor or of the folliculine as the causative agent of corporeal cancer.

Reverting, after this little digression, to our original investigations, the next step was to follow up our hyperplastic subjects of the 10 years prior to 1945. In all, 546 patients were invited for reexamination or sent queries. Unfortunately, due to post-war conditions, not more than 240 of them could be examined. Of these, 74,6 per cent claimed not to have had any complaints whatever, while 25,4 per cent had had disturbances of one or more bleedings. Hyperplasia was found to be associated with cancer of the body of the uterus in 10 cases, or 4,16 per cent ; ovarian cancer was encountered in 2,08 per cent, and collum cancer in 1,6 per cent. In other words, 19 out of 240 patients, i. e., 7,9 per cent, had developed carcinoma in the years following hyperplasia.

Prompted on the hand by the widely divergent results recently published and on the other hand by a desire to control our own findings, a new series of investigations was initiated in 1950, excluding of course all cases of hyperplasia that had been examined on previous occasions. These new investigations were extended to the apparently normal part of the endometrium encountered sometimes in the presence of cancer of the uterine body. From a total of 1177 microscopic sections, 205 showed cystic glandular hyperplasia, and 24 revealed adenocarcinoma of the body of the uterus. Concurrent hyperplasia and corporeal cancer were present in 7 cases, or 3,4 per cent ; a percentage almost identical

with that found in our examinations described in the preceding paragraph. 29,4 per cent of the reviewed 24 corpus cancer slides showed hyperplastic endometrium sheeds associated with adenocarcinoma. This rate closely approximates that established by NOVAK and YUI (1936), who encountered endometrial hyperplasia accompanying cancer of the body in 24,3 per cent of their cases.

It can be seen, then, that different methods of investigation applied to different groups have yielded almost identical results. From this it would appear that under certain circumstances folliculine undoubtedly has a part in the pathogenesis of cancer of the uterine body. Our investigations, further, seem to bear out the concept that cystic glandular hyperplasia is a lesion markedly predisposing to uterine cancer. Hyperplasia in our opinion is not preblastomatosis, but certainly a lesion which predisposes to cancer. We do not think that folliculine is a substance carcinogenic in women, that it is the cause of cancer of the uterine body, but we do think that some role is played by it in the development and subsequent growth of that type of cancer. That role may be a preparatory one, since the folliculine-stimulated abnormally proliferating epithelium is obviously more ready to transform into carcinoma upon the action of the unknown oncogenic agent than is epithelium at rest — or it may be one of stimulating the growth of an already existing cancer. In our view, then, folliculine should be regarded as a cocarcinogenic substance. Support seems to be afforded for this view, amongst others, by the latest cancer theory of ZILBER (1955) that malignant transformation is invariably preceded by hyperplastic proliferation, and by the finding of GREENE, BURROWS, and others, that spontaneous endometrial carcinoma in rabbits is commonly concurrent with hyperplasia.

It is still possible, of course, that some organic dysfunction (endocrine, metabolic, diencephalic), as yet unknown, lies concealed behind both the cancer of the body of the uterus and the hyperplasia, and that these two conditions are two different manifestations of the identical dysfunction.

Before proceeding to report the results of animal experiments which were undertaken to verify the correctness of our views, particularly those on the cocarcinogenic quality of folliculine, we feel that we have to controvert some of the most recent explicit negations in the literature for which, we believe, insufficient evidence has been put forward. The principal deficiency common to them is the failure to distinguish between menopausal and non-menopausal hyperplasia, since the inclusion of the latter leads necessarily to an erroneous ratio of hyperplasia to carcinoma. Among others, the latest publications of SCHRÖDER (1954), KOFLER (1954), WASCHKE (1955) suffer from this deficiency. Another feature in these papers which invites criticism, consists in that they declare to be unessential, or not higher than the average incidence of cancer of the body, such percentages of carcinoma as are actually several times the average incidence. SCHRÖDER (1954), for example, on finding 10 cases of corporeal cancer in 3596 patients with hyperplasia, maintains that this

ratio excludes any relationship between the two conditions, whereas, with the average 0,03 per cent incidence of corporeal cancer, the number of his combined cases gives nearly ten times the average incidence cancer of the body of the uterus, taking no account of the fact that his 3596 patients with hyperplasia were not all in the menopause. Even more interest attaches, from this angle, to KOFLER's report. He found hyperplasia combined with carcinoma and corporeal cancer concurrent with hyperplasia to occur in proportions almost identical with those established by us, yet he believes them explainable by chance alone. Reexamining his hyperplastic patients he encountered cancer of the body of the uterus in 0,6 per cent, which means that in his material the incidence of the association was twenty times the average rate, and would be substantially more had he included menopausal hyperplastics only. It is difficult to see how under these circumstances he can refuse the concept that an interconnection of hyperplasia folliculine, and cancer of the body of the uterus is quite possible.

Clearly, the problem is far from being solved, and it is regrattable that preconceived ideas should often influence the evaluation of results obtained, or that deficient statistical computations should underlie opinions.

Let us devote a few words to the regulation of oestrogenic effect. The role generally attributed to the ovary is that of secreting sexual hormones which act upon certain recipient organs (endometrium, vaginal epithelium) ; so while it is a producer of hormones, it is incapable of influencing their action, or that of hormones reaching the organism from without. With the passing years, numerous clinical observations have been forthcoming which discredit this theory. In our Department, CSILLAG, HAJDU, and SÁNDOR (1950) provided evidence that apart from the dependence of the recipient organs on the amount of oestrogens present in the organism, certain influences assert themselves in the latter, which inhibit oestrogenic effect. They proved experimentally that removal of the ovaries diminishes or even blocks this inhibition. Having recognised this inhibitive action of ovarian or other origin, the question now is whether it likewise asserts itself against the carcinogenic effect of oestrogens.

Our experiments, in which mature albino mice of our own bread were used, were carried out to study 1. whether oestrogens are conducive to the development of malignant tumours, and 2. whether castration plays a role in their formation.

In the first experimental series 4 groups of 10 mice each were given under the skin of the back injections of 15 mg of dibenzanthracene to produce the tumour, and the fifth served as control.

In the lst group, the animals received it dissolved in 0,5 ml of lard.

In the 2nd group, it was administered to animals treated with 0,2 γ of oestrogen every second day for a fortnight prior to the injection, and for six weeks thereafter.

In the 3rd group, castrated animals were used and they were given the same injection as the 1st group.

In the 4th group, again castrated animals were used and they were given injections of 0,2 γ of oestrogen daily until oestrus in them had become permanent, whereafter they received the carcinogenic agent in the same way as the first group. The daily oestrogen treatment was then continued for another 6 weeks.

The animals in the 5th group served as controls and were given an injection of 15 mg of pure lard each.

All mice used in the experiment were fed the same standard diet.

The first tumours appeared in about 5 to 6 month, and the animals were sacrificed 5 to 9 month after the beginning of the treatment.

Table I

15 mg of dibenzanthracene dissolved in 0,5 ml of lard, injected subcutaneously into the back of female mice

Oestrogen: 0,2 γ Number of test animals: 10 per group

1st	2nd	3rd	4th	5th group
Noncastrated	Noncastrated	Castrated	Castrated	Noncastrated controls
Dibenzanthracene	Dibenzanthracene + oestrogen	Dibenz-anthracene	Dibenzanthracene + oestrogen	Lard
2 tumours	4 tumours	2 tumours	6 tumours	0 tumours

It can be seen from Table I that tumours, which on histological examination proved to be fibrosarcoma, developed in all treated groups. They were least in number in the groups treated with the carcinogen alone, irrespective of whether they comprised castrated or noncastrated animals (1st and 3rd group). More of them developed in the group of noncastrated mice given oestrogen in addition to the carcinogen (2nd group). Most remarkable is that their number was the highest in the group of castrated animals treated with oestrogen plus carcinogen (4th group).

The evidence obtained in this experimental series seems to bear out the view that oestrogens are conducive to the development of malignant tumours and that they promote the action of the carcinogenic substance. This appears to confirm the concept that a cocarcinogenic effect is to be attributed to oestrogens. Of no less significance are perhaps the results which apparently point to an important part of castration the formations of tumours.

That this part is really one of consequence has been shown by another experimental series, involving 500 mice, in which it was attempted to transplant the tumours induced in the various manners described above. It was rather

striking to find that exclusively those induced in castrated animals were transplantable ; but these could then be transplanted through as many as 12 passages. This seems to indicate that certain changes in the internal environment of the organism in some way affect the biological properties of the tumour ; in other words, in the formation of these properties the general internal milieu is also at work, in addition to the carcinogenic agent.

Feeling that our results are questionable unless verified in a larger number of test animals, a third experimental series was initiated, again with 5 groups, but this time with 20 mice in each group. The results are presented in Table II.

Table II

15 mg of dibenzanthracene dissolved in 0,5 ml of lard, injected subcutaneously into the back of female mice

Oestrogen : 0,2 γ Number of test animals : 20 per group

1st	2nd	3rd	4th	5th group
Noncastrated	Noncastrated	Castrated	Castrated	Noncastrated controls
Dibenzanthracene	Dibenzanthracene + oestrogen	Dibenz-anthracene	Dibenzanthracene + oestrogen	Lard
5 tumours	12 tumours	10 tumours	14 tumours	0 tumours

Once more it can be seen that the malignant tumours were least in number in the noncastrated group treated with the carcinogen alone (1st group) ; twice as many developed in the one given dibenzanthracene plus oestrogen (2nd group). This series also brought supportive evidence for our views on castration inasmuch as upon the administration of the carcinogen in itself twice as many tumours developed among the castrated (3rd group) as among the noncastrated animals. Seeing these results it was almost natural to find the highest number of tumours in the group of the animals which had been castrated and pretreated with oestrogen before receiving the dibenzanthracene injection (4th group).

The action of oestrogenic substances and the effect of castration are perhaps still more convincingly evidenced by the data in Table III showing how the tumours arose in the order of time.

From Table III it can be seen that 8 tumours appeared in the 5th month after the beginning of the experiment, and that all of them developed in groups receiving some treatment in addition to a dibenzanthracene injection. In the 6th month, further 12 tumours arose, and again in the same groups. It was only in the 7th month that a single tumour developed in the group that had received nothing but the carcinogen, while in the other groups the same month brought out 10 further tumours. In other words, the group of noncastrated animals treated with carcinogenic substance alone produced a single tumour in the same

Table III

Chronological appearance of tumours
(Conditions of experiment identical with those in Table II)

	Groups of animals and treatment	Number of tumours developed in					Total number of tumours
		5th	6th	7th	8th	9th	
		month after beginning of experiment					
1.	Noncastrated Dibenzanthracene	—	—	1	1	3	5
2.	Noncastrated Dibenzanthracene + oestrogen	3	6	3	—	—	12
3.	Castrated Dibenzanthracene	3	1	2	2	2	10
4.	Castrated Dibenzanthracene + oestrogen	2	5	5	2	—	14

period during which altogether 30 tumours were induced in the groups that had either been castrated or received oestrogen in addition to dibenzanthracene (2nd group with 12, 3rd with 6, and 4th with 12 tumours). This certainly can be taken to mean that malignant growth is not only induced but also accelerated in its development by oestrogenic substances and castration, respectively.

Prompted by our result with female castrates we initiated a fourth experimental series with 60 male mice in 4 groups of 15 animals each.

1st group : noncastrated animals ; injection of the carcinogen alone.

2nd group : castrated animals ; injection of the carcinogen alone.

3rd group : noncastrated animals ; 0,5 γ. of neo-hombreol every second day for 8 days before and 6 weeks after injection of the carcinogen.

In the 4th group : castrated animals ; same treatment as in the 3rd group.

The results obtained in this series are presented in Table IV.

Table IV

15 mg of dibenzanthracene dissolved in 0,5 ml of lard, injected subcutaneously into the back of male mice

Testosterone : 0,5 γ of neo-hombreol — Number of test animals : 15 per group

1st	2nd	3rd	4th group
Noncastrated Dibenzanthracene	Castrated Dibenzanthracene	Noncastrated Dibenzanthracene-neo-hombreol	Castrated Dibenzanthracene neo-hombreol
6 tumours	5 tumours	3 tumours	4 tumours

These findings are rather interesting for they show that, unlike in females, in male mice castration fails to enhance tumour development, and that testosterone has apparently no effect upon carcinogenesis.

Summing up, we may state that experimental proof has been obtained of the carcinogenic action of oestrogens, and of the concept that castration plays an important role in the promotion of malignant growth in female mice. As has already been pointed out, this role may find its explanation in that the normally functioning ovary is somehow capable of neutralising the action of large amounts of oestrogen and, after castration, this ovarian neutralising capacity is of course lost. Obviously, the clue to the problem lies concealed in oestrogen metabolism since, at any rate by the evidence of our experiments, the carcinogenic effect of castration is less in male than in female mice. This seems to be quite natural, too ; after all, there is as yet nothing known to indicate that the testes would play the same part in the oestrogen metabolism of the organism of the male, which the ovary plays in that of the female organism.

From our studies we feel impelled to draw the practical conclusions, first, that even in or about the menopause very careful deliberation should precede the removal of the ovaries, secondly, that in treating climacteric symptoms the use of oestrogenic substances should be as far as possible avoided or at least reduced to a minimum. In fact, at the 2nd Department of Gynaecology we have made it the rule to remove the uterus in every woman past 35, should in spite of adequate treatment hyperplasia have recurred twice.

This paper is merely a contribution of data, and is presented with no illusions that it approaches a solution. The problem requires much further study, a modest part of which, e. g., hormonal paradoxy, and the effect of pregnancy on carcinogenesis, is already in progress.

Summary

Clinical observations covering 10 years, and animal experiments, undertaken to throw light on the interrelation of oestrogen, castration, and carcinogenesis are reported. They appear to confirm the cocarcinogenic property of oestrogen. The animal experiments direct attention to a role played by castration, which has not yet been mentioned in oncologic studies. Though not the preblastomatosis of corporeal cancer in the strict sense of the word, cystic glandular hyperplasia is definitely held to be a lesion predisposing to cancer of the body of the uterus. Conclusions drawn for clinical purposes are discussed.

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ИССЛЕДОВАНИЕ СВЯЗЕЙ МЕЖДУ ФОЛЛИКУЛЯРНЫМ ГОРМОНОМ, КАСТРАЦИЕЙ И КАРЦИНОГЕНЕЗОМ

Л. ВАЦИ

Автор излагает результаты своих исследований, проведенных в течение 10 лет как в клинике, так и в опытах над животными, в целях выяснения связи между фолликулярным гормоном, кастрацией и карциногенезом. Исследования автора подтверждают повидимому карциногенное свойство фолликулярного гормона. Его опыты над животными обращают — кроме этого — внимание на до сих пор еще неизвестную онкологическую роль кастрации. На основании своих опытов автор того мнения, что железисто-кистозная гиперплазия, если и не является прибластоматозом рака шейки матки в строгом смысле слова, то ее все же безусловно можно рассматривать как изменение, создающее склонность в развитию рака тела матки. В заключении автор излагает выдвигаемые из его исследований практические заключения.

UNTERSUCHUNG DER ZUSAMMENHÄNGE ZWISCHEN FOLLIKELHORMON, KASTRATION UND KARZINOGENESE

L. VÁCZY

Es werden die Resultate 10jähriger klinischer und tierexperimenteller Untersuchungen der Zusammenhänge zwischen Follikelhormon, Kastration und Karzinogenese mitgeteilt. Die Untersuchungen scheinen die kokarzinogene Eigenschaft des Follikerhormons zu bestätigen. Die Tierversuche lenken die Aufmerksamkeit ausserdem auf die bisher unbekannte onkologische Rolle der Kastration. Auf Grund des Untersuchungen kann die glandulärzystische Hyperplasie, wenn auch nicht in strengem Sinne als Präblastomatose des Gebärmutterkörperkrebses, so doch unbedingt als eine zur Entstehung jenes Tumors disponierende Veränderung betrachtet werden. Zum Abschluss werden die aus den Untersuchungen sich ergebenden praktischen Folgerungen erörtert.

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