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THE TUMOURIGENIC EFFECT OF OESTROGENS, TESTOSTERONE AND CASTRATION

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(Received September 6, 1954)

In a previous study of the effect of oestrogens upon the genesis of malignant tumours [5] it was found that these substances promote the formation of malignant tumours, or intensify the action of carcinogenic substances, confirming the investigators stating that oestrogens possess co-carcinogenic properties. We have observed, in addition, that also castration has an important role in the development of tumours. It was namely found that a considerably greater number of tumours had been formed under the influence of carcinogenic and oestrogenic substances in castrated animals than in non-castrated ones. The reliability of these results was, however, seriously impaired by the fact that a small number of animals had only been subjected to the experiments. It was, therefore, imperative to repeat the experiments in question with groups composed of a greater number of animals, in order to check the reliability of our findings.

The purpose of the present paper is to report the results obtained by repeating our earlier experiments and also some findings yielded by a new experimental series investigating into the same problem. In the experiments under review the same methods were naturally employed as in the previous ones. 100 sexually mature female albino mice of our own stock have been used in the study. The animals were divided into 5 groups of 20 animals each.

The 1st group consisted of *non-castrated* animals, into the back of which 15 mg of dibenzanthracene dissolved in 0,5 ml of lard was injected subcutaneously.

The 2nd group, too, consisted of *non-castrated* animals; before injecting the above amount of dibenzanthracene they had been treated with 0,5 γ of oestrogen every second day for a fortnight; the administration of oestrogen was continued for six weeks after the injection of carcinogenic agent.

The 3rd group was composed of *castrated* mice which received dibenzanthracene injections in the same doses as the animals of the first two groups.

In the 4th group constant oestrus had been brought about in *castrated* mice by administering 0,5 γ of oestrogenic substance every second day; then

15 mg of dibenzanthracene was injected, and the administration of oestrogen continued for six weeks.

Animals of the 5th group, serving as *control*, received identical doses of pure lard subcutaneously injected.

During the experiments, the animals were kept on the same diet as the rest of our stock of mice.

The first tumours appeared about 5 to 6 months after the treatment, as in our previous experiments. The animals were killed 5 to 9 months after the beginning of the treatment. The experiment was terminated in the 9th month. The tumours and the internal organs of the animals were histologically examined. Diagnosis of the tumours was established on the basis of histology.

Except the control-group, tumours have developed in all of the groups, and histological examination showed them to be fibrosarcoma.

While the majority of the tumours occurred underneath the skin, metastases were found in the abdominal lymphglands, the liver and the kidneys.

TABLE I

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

Oestrogen 0,5 γ
Number of test animals: 20 per group

I.	II.	III.	IV.	V.
Non-castrated Dibenzanthracene	Non-castrated Dibenzanthracene Oestrogen	Castrated Dibenzanthracene	Castrated Dibenzanthracene Oestrogen	Non-castrated Controls. Lard
5 *tumours*	12 *tumours*	10 *tumours*	14 *tumours*	0 *tumours*
6 abscesses	5 abscesses	5 abscesses	3 abscesses	4 abscesses
1 peritonitis	3 normal	2 toxic	1 toxic	3 atrophies
8 normal	—	3 normal	2 normal	13 normal

The results of the experiments are tabulated in Tables I and II. The figures listed in the Tables confirm the correctness of our previous findings in every point. As evident from Table I, the smallest number of tumours arose in the non-castrated group treated with carcinogenic substance only (1st group). Twice as many tumours were formed in the group treated with oestrogen and dibenzanthracen (2nd group). Castrated animals which had been treated with carcinogenic substance only (3rd group) developed twice as many tumours than the similarly treated non-castrated ones. It seems, therefore, that oestrogens really act as co-carcinogens, and that the findings established on the strength of our previous experiments were correct. After such antecedents it was only natural that the highest number of tumours occurred in those animals (4th group)

which had undergone castration before treatment with carcinogens and had, in addition received preliminary treatment with oestrogens.

TABLE II

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

Groups of animals		Number of months since beginning of experiment					Total
		5.	6.	7.	8.	9.	
I.	Non-castrated Dibenzanthracene	—	—	1 tumour	1	3	5
II.	Non-castrated Dibenzanthracene Oestrogen	3 tumours	6	3	—	—	12
III.	Castrated Dibenzathracene	3 tumours	1	2	2	2	10
IV.	Castrated Dibenzanthracene Oestrogen	2 tumours	5	5	2	—	14

The effects of oestrogenic substances and castration are still more clearly verified by the data of the 2nd Table. Table II illustrates the chronological appearance of the tumours. It shows that 8 tumours appeared in the 5th month after the beginning of the experiment. Three developed in the non-castrated animals that had been treated with cancerogenic substance and oestrogen (2nd group), three in the castrated animals treated with cancerogenic substance only (3rd group), while two of the tumours developed in the castrated mice treated with both cancerogenic substance and oestrogen (4th group). In the 6th month, 12 tumours appeared, all of them in groups 2 to 4, i. e. in the animals that had been subjected to treatment. (There were three tumours in the 2nd group, two in the 3rd and five in the 4th group.) The first tumour was brought about only in the 7th month in the group treated merely with cancerogenic substances (1st group), and even this time with only one occurrence while, during the course of the same month another ten tumours developed in the other groups. This means that during the time required to induce one single tumour in the non-castrated animals, to which only a cancerogenic agent and no oestrogen had been administered, no less than thirty tumours were observed in the other three groups (twelve in the 2nd group, six in the 3rd and 12 in the 4th group). It would seem therefore that oestrogenic substances and castration not only promote malignant growth but also hasten its development.

The observed effect of castration made us to study it in *male animals* as well. 60 male mice, divided into 4 groups of 15 animals each, served as the subjects of this experiment.

Group I consisted of *non-castrated* animals, treated with carcinogen in the same manner and in the same doses as in the first experiment.

Group II was composed of *castrated* animals treated with carcinogen.

Group III included *non-castrated* animals which, before being injected with the carcinogenic substance, received Neo-Hombreol.

Group IV comprised *castrated* animals into which carcinogen was injected after a preliminary treatment with Neo-Hombreol.

We began the administration of Neo-Hombreol to the animals of Groups III and IV eight days before the injection of dibenzanthracene and continued it for six more weeks thereafter; the dose of the testosterone was 0,5 γ every second day.

TABLE III

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

I.	II.	III.	IV.
Non-castrated Dibenzanthracene	Castrated Dibenzanthracene	Non-castrated Dibenzanthracene Neo-Hombreol	Castrated Dibenzanthracene Neo-Hombreol
6 *tumours*	5 *tumours*	3 *tumours*	4 *tumours*
4 abscesses	6 abscesses	6 abscesses	5 abscesses
2 toxic	2 toxic	3 toxic	4 toxic
3 normal	2 normal	3 normal	2 normal

It is evident from Table III that castration of male animals is not followed by enhanced development of tumour such as is the case if females are castrated, since an approximately identical number of malignant growths was observed in both castrated and non-castrated animals. Nor could we detect any carcinogenic effect that would have been attributable to testosterone, as the tumourigenic action of dibenzanthracene was in no way influenced by treatment with Neo-Hombreol.

We attribute especial significance to the results of the experiments described because they seem to throw new light on the oncological role of castration. Our two series of experiments show that castration exerts a serious blastomatogenic effect if performed on female animals and none if performed on male. Extensive investigations will naturally be necessary to elucidate this problem. Some of them, such as a study of the paradoxical hormonal effect in castrated and non-castrated animals, or of the effect exerted by an increased dose of testosterone, are already in progress.

Two more phenomena observed in the course of the experiments are worth of note. (i) Ascites was frequently formed in addition to tumours. It may be of interest that, both in our previous and the present experiments, ascites occurred in castrated mice only. (ii) As mentioned in a previous paper [2] only such tumours could be transplanted which had been induced in castrated animals.

To sum up the results of the present study, they have corroborated those of our previous experiments in every respect. They too seem to prove that oestrogenic substances act as co-carcinogens, and that castration, performed on females, plays an important part in the promotion of malignant growth. We think that this effect of castration might be due to the fact that, as has been demonstrated by Csillag, Hajdu and Sándor [1], the normally functioning ovary is somehow capable of neutralizing the action of a great amount of oestrogenic substances. Castration in our experiments probably acted by eliminating that retarding action of the ovary. The correctness of our assumption regarding the said role of castration, viz. that it is the metabolism of oestrogenic substances which lies at the root of the problem, seems to be confirmed by the results of our experiments on male animals. Castration of males had no such blastomatogenic effect as in females. This must seem natural after what has been expounded above, since we know of no literary data according to which the testes had a same influencing effect to the oestrogenic metabolism taking place in male organisms, too, as that of ovary in females.

The results of our above described recent experiments seem to justify the opinion expressed in our previous paper that any unwarranted removal of the ovary should be considered very carefully even at the time of menopause. Our experiments have further corroborated our opinion that, when treating climacteric and praeclimacteric symptoms the use of oestrogenic substances should be reduced to a minimum.

Summary

The effect of oestrogenic substances, testosterone, and castration upon the development of tumours induced in female and male mice by dibenzanthracene has been investigated. Oestrogenic substances have been found to intensify the tumourigenic action of dibenzanthracene. Castration of female mice had the same effect, whereas in male animals castration did not seem to promote malignant growth. The application of testosterone also failed to reveal tumourigenic properties in the doses administered.

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(Abbreviation : M. N. L. = Magyar Nőorvosok Lapja = Review of Hungarian Gynaecologists.)

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ДЕЙСТВИЕ ЭСТРОГЕННЫХ ВЕЩЕСТВ, МУЖСКОГО ПОЛОВОГО ГОРМОНА И КАСТРАЦИИ НА ОБРАЗОВАНИЕ ОПУХОЛЕЙ

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Авторы исследовали на самках и на самцах мышей действие эстрогенных веществ мужского полового гормона и кастрации на образование опухолей, индуцированных дибензантраценом. Они выявили, что эстрогенные вещества повышают вызывающее опухоли действие дибензантрацена. На самках мышей кастрация также вызвала значительное повышение действия дибензантрацена. У самцов мышей авторам не удалось наблюдать подобного действия кастрации. Действие мужского полового гормона в применяемом авторами количестве на образование опухолей также не удалось выявить.

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