Strain Differences in Response to Diethylstilbestrol and the Induction of Mammary Gland and Bladder Cancer in the Rat

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For the past 20 years, the field of experimental cancer research has been largely dominated by studies on the occurrence, production, or prevention of mammary cancer in the mouse. The development through inbreeding and selection of numerous strains of mice in which these neoplasms occur spontaneously with a relative high frequency and the economy of feeding and housing mice in preference to other laboratory animals have been factors contributing to this situation. So predominate is this particular form of malignant disease that mice that fail to develop it have become known as non-tumor mice, irrespective of any further tumor history or the ease with which they respond to various tumor-inducing agents. The controversy over the hereditary nature of these tumors was largely explained by the discovery of Little and his co-workers (8) and of Korteweg (12) of an important extrachromosomal or milk influence. This was demonstrated by significant differences in the incidence of mammary tumors in the F1 progeny of reciprocal crosses between high and low mammary cancer stocks. Bittner (2, 3) demonstrated further, that foster nursing of the progeny of cancerous mothers by low mammary cancer stock mothers largely prevented the occurrence of mammary cancer in these foster-nursed females. More recently Bittner (4) has shown that feeding the filtrate from macerated lactating mammary glands obtained from mice of high mammary cancer stock caused the foster-nursed daughters to develop mammary cancer 8 to 10 months later. Green, Moosey and Bittner (9) have further demonstrated the production of antibodies and antiserums, which are capable of neutralizing or inactivating the centrifugates of mouse mammary cancer, while antiserums produced similarly in response to normal mouse tissue are ineffective. Thus an important factor in mouse mammary cancer development appears to be a self-perpetuating, exogenous body analogous to a virus.

Early experiments in castration demonstrated the relationship between the ovarian hormones and the development of mammary cancer in the mouse. Prepubertal ovariectomy inhibited the development of mammary tissue and prevented the occurrence of mammary cancer while the injection of estrogens caused the mammary cancers to appear earlier than they did in untreated females. Lacassagne (10, 11) showed that the injection of estrogens in male mice from birth or an early age caused them to develop mammary cancer in the same frequency as their sisters. These findings have been confirmed by many investigators as indicated in a recent survey of the literature on the subject by Gardner (7). It seems however, that the female sex hormones alone are insufficient to cause the development of mammary cancer in some mice that lack the hereditary factors. Thus the development of mammary cancer in the mouse appears to be dependent upon three separate etiological factors; namely, hereditary, extrachromosomal or milk, and hormonal. This anomalous situation has given impetus to a search for similar factors in the etiology of other types of neoplasia in the mouse and of mammary cancer in other species, including man. So far, the search has failed to identify in other species a factor analogous to the milk influence in mammary cancer of mice.

The rat has been considered peculiarly insusceptible to mammary cancer but, although Curtis, Bullock and Dunning (5) reported only 2 mammary cancers in a colony of nearly 9,000 female rats of tumor age, the animal has not proved resistant to the induction of mammary cancer by excessive estrogenic stimulation. The contrast between the relatively low frequencies of induced mammary cancer reported by McEuen (13) and Eisen (6) and the high frequency obtained by Geschickter and Byrnes (8) and Nelson (14) would suggest the operation of

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possible hereditary factors, since these investigators employed different strains of rats. McEuen reported only 2 mammary cancers in 12 rats that survived for 500 days with daily injections of 30 mg of estrone and Eisen obtained 2 mammary cancers in 103 rats that survived for 242 days with implantations of 1 to 20 mgm. of crystalline estradiol dipropionate in paraffin. In contrast, Nelson observed 63 mammary cancers in 103 treated rats that survived 300 days and longer. Geschickter and Byrnes reported 202 rats with mammary cancer from 555 rats treated with various doses of estrone and stilbestrol and prescribed that, to produce mammary cancer in the rat, the dose of estrogen must be well beyond the physiologic limit (10 or more times the threshold dose) and the treatment continuously applied for a period of months (30 or more times the duration of normal estrus). Since the dose of estrogen employed by McEuen and by Eisen met these requirements, there would seem to be some fundamental difference in the rats used for these investigations. Obviously, unphysiological estrogenic stimulation is a factor in the etiology of mammary cancer in the rat as well as in the mouse. Here would seem to be an excellent opportunity to determine further, whether or not hereditary or milk factors predispose rats to estrogen-induced mammary cancer.

It is the purpose of the present paper to report the response of 3 inbred lines of rats to unphysiological stimulation from diethylstilbestrol. A later communication will deal with the response of reciprocal F1 hybrids between 2 of these lines to an effective mammary cancer-inducing dose of diethylstilbestrol.

MATERIALS AND METHODS

Pedigreed rats of 3 distinct lines, Fischer line 344, Copenhagen line 2331, and A × C line 9935, were used for this investigation. They received the laboratory stock diet (Friskie Dog Pellets) supplemented with a green vegetable once a week. The cancer history of the ancestors of these three lines is known for 40, 31 and 27 brother-by-sister generations, respectively, and no spontaneous mammary cancers were observed. Each series consisted of 30 males and 30 females from each line, which at the start of the experiment were between 3 and 4 months of age.

In Series I, pellets weighing between 15 and 25 mgm. of compressed crystalline diethylstilbestrol1 were implanted in the scapular region by means of nasal forceps inserted through an incision in the skin of the lower back. The incision was closed with a wire staple. The rats were weighed and inspected for mammary tumors every 2 weeks. Any rat that gained appreciably for 2 successive weightings, or any male in which the testicles descended, or any female found to be in a diestrous phase, was reimplanted with another pellet of diethylstilbestrol. At death any remaining pellet was removed, weighed and subtracted from the weight of diethylstilbestrol that had been administered to the rat. At the postmortem examination, a thorough inspection for gross tumors was made and gross sections of mammary gland, thymus, liver, kidney, adrenals, urinary bladder, sex glands, and pituitary were preserved for microscopic examination.

In Series II, a similar group of rats were implanted in the scapular region with pellets composed of 75 per cent cholesterol and from 4 to 15 mgm. of diethylstilbestrol. The diethylstilbestrol in this series was much more slowly absorbed and no reimplantations were necessary to keep the rat in a constant state of hyperestrinism for the remainder of its life. It was, however, impossible to determine the amount of diethylstilbestrol actually absorbed from the pellets because at the death of the animal, after many months in the rat, some of the pellets weighed the same or more than when they were implanted. Otherwise, these rats were treated similarly to those of Series I.

RESULTS

The results are summarized briefly in Tables I and II and shown graphically in Figs. 1 and 2. The rats of Series I represented in Table I and Fig. 1 showed considerable variation in survival and in the absorption of diethylstilbestrol. The 17 Fischer line 344 females on which complete records were obtained survived for an average of only 67 days and had absorbed 19 mgm. of crystalline diethylstilbestrol or an average of 0.26 mgm. per rat per day. The average body weight fell from 120 gm. to 110 gm. in the first 2 weeks and remained low. One female survived for 143 days, having absorbed 34 mgm. of diethylstilbestrol. All of these females died with pyometra and in most cases peritonitis was evident. The Fischer line 344 males lived twice as long, or an average of 136 days, absorbing an average of 29 mgm. of diethylstilbestrol at the rate of 0.2 mgm. per rat per day. Their average body weight fell from 167 to 144 gm. within 2 weeks and only 4 of the rats survived for 6 months. The Copenhagen line 2331 and A × C line 9935 rats absorbed the diethyl-

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1Supplied through the courtesy of Dr. D. F. Robertson of Merck and Co., Rahway, N. J.
Fig. 1.—Survival period and tumor history of rats of each strain with pellets of crystalline diethylstilbestrol implanted in subcutaneous tissues of scapular region. (Each rat is represented by a bar, length of which shows the period of survival in days, with postmortem findings indicated by proper shading.)
FIG. 2.—Survival period and tumor history of rats of each strain with cholesterol pellets containing 25 per cent diethylstilbestrol implanted in subcutaneous tissues of the scapular region. (Each rat is represented by a bar, length of which shows the period of survival in days, with post-mortem findings indicated by proper shading. In the cases where rat had mammary cancer and another of the pathological conditions, the latter is indicated by a box with proper shading connected by an arrow.)
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stilbestrol more slowly and survived the treatment longer. There was less difference between the A × C males and females, but the female had a longer average survival because one female lived for 406 days, as shown in Fig. 1. The average survival period was 167 days for the males and 186 days for the females, while the former absorbed 24 mgm. of diethylstilbestrol and the latter an average of 25 mgm. The average body weight dropped from 142 gm. to 117 gm. in the males and in the females from 116 gm. to 104 gm. within 2 weeks after the pellets were implanted. The Copenhagen line 2331 males survived the treatment longer than any of the other rats—an average of 289 days compared with 200 days for the females. The former absorbed 38 mgm. of diethylstilbestrol and the latter 31 mgm. The average body weight of the males fell from 122 gm. to 94 gm. in the first 2 weeks and that of the females from 115 gm. to 94 gm. Eleven males and 2 females survived for more than a year.

No mammary cancers were observed in these rats, although considerable hyperplasia of the mammary tissue was noted in 13 A × C females, also in one Fischer male and 2 Copenhagen females. The most conspicuous differences were observed in lesions of the pituitary, liver and bladder. The Fischer line 344 males and females without exception had large hemorrhagic pituitary adenomas, which in some cases weighed as much as 500 mgm. The Copenhagen line 2331 rats had enlarged pituitaries, which rarely became hemorrhagic and averaged less than 100 mgm., although they lived significantly longer than the Fischers and absorbed more diethylstilbestrol. The pituitaries in the A × C line 9935 rats were intermediate, rarely obtaining the size of those in the Fischers and usually exceeding those of the Copenhagen. A previous publication (16) noted a similar difference in response of the pituitary and also a distinct difference in the adrenals of A × C and Fischer castrated males to daily injections of 1 mgm. of diethylstilbestrol. The characteristic difference between the pituitary adenomas in the Fischer line 344 and the Copenhagen line 2331 rat is shown in Fig. 3. The albino rat on the right, a Fischer line 344 male, had absorbed 33 mgm. of diethylstilbestrol in 170 days. The pituitary in this rat weighed 400 mgm. The rat on the left was a Copenhagen female which had absorbed 34 mgm. of diethylstilbestrol in 183 days. The pituitary weighed 60 mgm. The photograph also shows the pellets in situ.

One of these large hemorrhagic pituitary adenomas from a Fischer line 344 male was transplanted into the subcutaneous tissues of 6 males of the same line in which diethylstilbestrol pellets had been previously implanted. All of the grafts grew progressively until the hosts died from the effects of the rapid absorption of diethylstilbestrol with large pituitaries in situ. Some of the subcutaneous growths attained a diameter of 1.5 cm. and weighed nearly 1 gm. A section through one of these subcutaneous growths is shown in Fig. 9. It has the characteristic large sinuses filled with red blood cells, is quite cellular with many mitoses and in many respects resembles a neoplasm, but it failed to grow upon transplantation into untreated rats of the same inbred line.

Extensive fatty infiltration of the liver was observed in 16 of the Fischer line 344 males and in 4 of the females. Fatty livers were not found in treated rats of the other 2 lines nor in untreated Fischer rats. A section through one of these livers is shown in Fig. 7.

The most striking lesion was observed in the bladder of the Copenhagen line 2331 male rats which had been treated for 6 months and more. The bladder was distended up to 10 times its normal size, and in many instances was packed with faceted calculi. These, usually smooth and rounded, but sometimes rough and crystalline, proved to be chiefly magnesium ammonium phosphate like those reported by Benjamin, Wilson and Leahy (1) for a-estradiol-treated rats. The walls of the bladder were usually thickened and papillated and in 14 of the 16 males with calculi, contained one or multiple papillomas. One female Copenhagen had bladder calculi and papilloma and two A × C males also had bladder calculi.
FIG. 3.—Pituitary adenoma and diethylstilbestrol pellets in situ. White rat = Fischer line 344 male which absorbed 33 mgm. of crystalline diethylstilbestrol in 170 days. Agouti rat = Copenhagen line 2331 female which absorbed 34 mgm. of crystalline diethylstilbestrol in 183 days.

Fig. 4.—Calculi exposed in the bladder of an A X C line 9935 rat 308 days after receiving a cholesterol pellet containing 12 mgm. of diethylstilbestrol.

Fig. 5.—A X C line 9935 rats with induced mammary cancers. At right, female after 371 days with 5 mgm. of diethylstilbestrol in cholesterol pellet. At left, female after 377 days with 7.5 mgm. of diethylstilbestrol in cholesterol pellet.

Fig. 6.—A X C line 9935 female with induced lymphosarcoma 322 days after receiving 4 mgm. of diethylstilbestrol in cholesterol pellet.
Fig. 7.—Section of a fatty liver from a Fischer line 344 rat which absorbed 33 mgm. of diethylstilbestrol in 177 days. Mag. X 125.

Fig. 8.—Section of a bladder papilloma in a A X C rat 308 days after it received 12 mgm. of diethylstilbestrol in a cholesterol pellet. Mag. X 50.

Fig. 4 shows one of these bladders with the calculi exposed and Fig. 8 shows a section through one of the papillomas. Unlike the urinary calculi reported by Wilson, Benjamin and Leahy (19) in rats, and Schenken, Burns and McCord (15) in α-estradiol-treated C3H mice, these did not appear to be associated with inflammatory changes in the urinary tract. No calculi were found in the kidneys...
or ureters and pathological changes were no more frequent in the kidneys of these rats than in those of the treated rats of the 2 other lines.

The rats of Series II, which received the pellets composed of 25 per cent diethylstilbestrol and 75 per cent cholesterol tolerated the treatment much longer as shown in Table II and Fig. 2. Half of the Fischer line 344 males and 4 of the females survived for a year. The majority of the rats of the two other lines lived more than a year and 2 A X C and 4 Copenhagen rats survived for more than 2 years. The Fischer and A X C females lost an average of only 2 to 4 gm. during the first 2 weeks after the pellets were implanted whereas the Copenhagen females lost 10 gm. The males lost from 16 to 20 gm. during the interval, but their weight gradually increased after the first 4 months. Very few fatty livers were observed, 2 in Fischer line 344 males, 1 in a Fischer and 1 in A X C rats. The difference between the Fischer line 344 and A X C line 9935 rats is partly attributable, as shown in Fig. 2, to the differences in survival, but not entirely. The tumors observed in the Fischer line 344 rats were all solitary as shown in Table II, but in the A X C rats most of the tumors were multiple. Typical examples are shown in Fig. 5. The rat at the left of the photograph had 6 probably independent tumors and the one on the right had 3. Fourteen independent tumors were found in one female; and many of the rats had additional areas of extreme hyperplasia with ductal infoldings and squamous metaplasia as shown in Fig. 10, which were considered pre-cancerous lesions. In the 22 A X C line 9935 female tumor-bearers, 89 tumors were observed or an average of 4 to the rat. In the 17 A X C males 39 tumors were described or an average of 2 to the rat. One A X C male had 5 gross tumors and one

<table>
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<th>No. of rats</th>
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<th>Strain</th>
<th>Av. no. days until death</th>
<th>Av. amt. of stilbestrol (mgm.)</th>
<th>Average pituitary wt. (mgm.)</th>
<th>No. of rats with mammary cancer</th>
<th>No. of rats with bladder calculi</th>
<th>No. of rats with cancer</th>
<th>No. of rats with bladder cancer</th>
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Table II: Number of Rats of Each Strain, Average Dose of Diethylstilbestrol in Cholesterol, Average Survival, and Number of Rats with Mammary Gland Cancer and Bladder Calculi and Cancer

an A X C female. The pituitaries were enlarged but not as consistently or as rapidly, or to as great a magnitude as in the rats of the other series.

Bladder calculi were observed in 22 or 73 per cent of the 30 Copenhagen line 2331 males and in 8 or 30 per cent of the 28 females of this line. The first were observed in a male that died 231 days after the pellet was implanted. In Series I, the calculi were found consistently in the Copenhagen line 2331 males after 180 days. Six A X C line 9935 males and 1 female also had calculi and a few small crystals were observed in the bladder of 3 of the Fischer line 344 females. Bladder papillomas and grade I squamous cell cancer were observed in 16 of the Copenhagen line 2331 males and 6 of the females which had calculi. Two A X C line 9935 males and 1 female also had bladder papillomas and cancer.

In Series II, mammary cancer occurred in 22 or 85 per cent of the females and in 17 or 80 per cent of the males of A X C line 9935. One Fischer line 344 female and 5 Fischer males also had mammary cancers. No mammary cancers were found in the treated Copenhagen males or females, although they outlived the Fischer line 344 rats by several months and lived fully as long as the other which was identified by microscopic examination of the mammary tissue. Fig. 6 shows an A X C female rat with a lymphosarcoma which arose in the superficial lymph nodes of the left groin breast and metastasized to the other superficial lymph nodes, mediastinum and lungs. Fig. 14 shows a section through this tumor. The mammary cancers\(^3\) in the A X C rats included 107 papillary cystic adenocarcinomas (Fig. 11), 11 adenocarcinomas and squamous cell cancers or adenocanthomas (Fig. 13), 3 solid carcinomas (Fig. 12), 2 solid carcinomas with papillary areas and 4 that were unclassified. The mammary tumors in the Fischer line 344 rats included 1 solid carcinoma, 1 interductal carcinoma and 4 papillary cystic adenocarcinomas.

No pellet was found in the A X C female shown in Fig. 2, which outlived the others and died without a mammary cancer. Scantily developed mammary tissue and a small pituitary (10 mgm.) suggested that the pellet had ulcerated out a considerable time before. Postmortem examination revealed an extensive osteosarcoma of the uterus.

\(^3\)The authors gratefully acknowledge indebtedness to Dr. Martha E. Madsen for assistance in classifying the tumors.
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Fig. 11.—Papillary cyst adenocarcinoma from an A × C female rat, 348 days after it received 4 mgm. of diethylstilbestrol in a cholesterol pellet. Mag. X 150.

Fig. 12.—Mammary carcinoma from a Fischer line 344 female rat, 302 days after it received 7 mgm. of diethylstilbestrol in a cholesterol pellet. Mag. X 125.

Fig. 13.—Adenocanthoma from an A × C female rat, 349 days after it received 4 mgm. of diethylstilbestrol in a cholesterol pellet. Mag. X 50.

Fig. 14.—Lymphosarcoma from an A × C female rat, 322 days after it received 4 mgm. of diethylstilbestrol in a cholesterol pellet. Mag. X 125.

with metastases to the lung and lymph nodes, which may have been related to the previous estrogenic stimulation. Another A × C female had a mixed tumor (chondrosarcoma and adenocarcinoma) of the ovary and a third, a carcinoma of the adrenal cortex. The latter probably resulted from the treatment, as it is a common sequel to estrogenic treatment in another strain of rats. Two A × C females had benign tumors of the thymus and 1 a lymphosarcoma of the ileocolic mesentery, which were probably unrelated to the treatment, since they occur in untreated rats of this strain.

Two Fischer line 344 males had adenoma of the adrenal cortex, 1 an adenocarcinoma, and another had a hepatoma. A lymphosarcoma of the ileocolic mesentery was observed in 1 Fischer male, and a Fischer line 344 female had a squamous carcinoma.
of the left ear, which were probably unrelated to the treatment.

Aside from the bladder carcinomas previously mentioned in the Copenhagen line 2331 rats, 1 female had a myosarcoma of the uterus; 1 male, a benign tumor of the thymus; 1 male, a lymphosarcoma of the ileocolic mesentery; and 1 male, a lymphocytic leukemia. The 3 last-mentioned neoplasms were probably unrelated to the treatment, although leukemia and lymphosarcoma are rare in untreated rats of this line.

**DISCUSSION**

Comparison of the results of Series I and II show that a slow continuous absorption of diethylstilbestrol is an effective mammary cancer incitant in some strains of rats, whereas a cyclical or more rapid absorption of even larger doses with a short intervening rest period is ineffective in rats of the same inbred line. Only 5 A X C line 9935 females and 3 A X C line 9935 males of Series I survived as long as the latent period previous to the observation of the first gross tumors in A X C rats of Series II, but no tumors could be identified by microscopic examination of their mammary tissue. These rats had absorbed from 20 to 39.1 mgm. of diethylstilbestrol. In a subsequent series, 4 A X C line 9935 rats survived for a year or more after the implantation of a single 20 to 25 mgm. pellet of crystalline diethylstilbestrol, plus 2 per cent methyl cellulose used as a binder without developing any mammary tumors.

The difference in response between the rats of the Copenhagen line 2331 and those of the other 2 lines that were tested, may be related to the manner of excreting the diethylstilbestrol and the formation of urinary calculi, or to the pre-existing disturbance in metabolism. However, the physiological processes resulting in formation of bladder calculi and bladder neoplasms in one line and mammary neoplasms in the other two are not mutually exclusive, as shown in Fig. 2, by 4 A X C rats with mammary cancer and bladder calculi. The mammary tissue of the Copenhagen rats of both series was less well developed than that of the rats of the two other lines, but areas of hyperplasia with lactating dilated ducts were commonly found and a few lesions which could be considered as precancerous were also observed. The mammary tissue of the Fischer line 344 rats seemed to be even more copiously developed than that in the A X C rats which responded with the higher percentage of mammary cancers. Possibly another estrogen or dose might reverse the reactions of these rats. For α-estradiol (17), the Fischer line 344 rats showed the highest threshold for vaginal estrus and an impaired ability for hepatic estrogenic inactivation, while the Copenhagen line 2331 rats exhibited a high threshold for vaginal estrus and the greatest ability for hepatic inactivation. The incomplete data on the estrone treatment of rats of these three strains, however, indicate a response similar to diethylstilbestrol. The observations recorded here clearly indicate constitutional differences in response to diethylstilbestrol and in the incidence of mammary gland and bladder cancer in the rat. That these variations are dependent upon genetically determined physiological differences in the absorption, utilization or excretion of diethylstilbestrol, rather than gene differences specifically related to cancer susceptibility, is also indicated.

**SUMMARY**

1. Pellets of compressed crystalline diethylstilbestrol weighing 15 to 25 mgm. were implanted in the scapular region of 30 rats of both sexes of each of 3 distinct inbred lines and were replaced individually as soon as the previous pellet was known to be completely absorbed.

2. The rats of the 3 lines varied in survival and in the absorption rate of the diethylstilbestrol. Rats of Fischer line 344 succumbed first after the most rapid absorption of the hormone. Females of this line lived an average of only 67 days and absorbed an average of 19 mgm. per rat. The males survived an average of 136 days and absorbed 29 mgm. of diethylstilbestrol per rat. The Copenhagen line 2331 males survived for 289 days and the females for 200 days, having absorbed an average of 38 and 30 mgm. of hormone, respectively. The rats of A X C line 9935 were intermediate; the males survived for 167 days and the females for 186 days, in which time the average absorption of diethylstilbestrol was 24 and 25 mgm. per rat.

3. The most conspicuous pathological lesions included pituitary adenomas, fatty livers, and bladder calculi and papillomas. Pronounced strain differences were observed in the expression of these lesions. The pituitaries in the Fischer rats averaged 300 and 400 mgm. respectively in males and females, and only 98 and 61 mgm. in Copenhagen males and females, and were intermediate in the A X C rats. Fatty livers were confined to Fischer rats, and with 3 exceptions, the bladder calculi and papillomas were confined to Copenhagen male rats.

4. Pellets of 75 per cent cholestrol containing 4 to 15 mgm. of diethylstilbestrol were implanted in the scapular region of a second and similar series of
rats and no reimplantations were necessary to keep the rats in a constant state of hyperestrinism for the remainder of their lives.

5. The average survival period for the Fischer line 344 rats was increased to 200 days for the females and 367 days for the males with the more slowly absorbed diethylstilbestrol. The A × C males lived an average of 388 days and the females survived 528 and 499 days, respectively.

6. Mammary cancer was observed in 17 or 80 per cent of the A × C males, in 22 or 85 per cent of the A × C females. Only 1 or 17 per cent of the Fischer line 344 females and 5 or 22 per cent of the Fischer line 344 males had mammary cancer.

7. No mammary cancers were observed in treated male or female Copenhagen line 2331 rats but 16 or 62 per cent of the males and 6 or 29 per cent of the females had either bladder papillomas or squamous cell cancer associated with urinary calculi.

8. The mammary cancers induced in Fischer line 344 and A × C line 9935 rats by slowly absorbed diethylstilbestrol included 111 adenocarcinomas, 11 adenocarcinomas and squamous cell cancers or adenoacanthomas, 4 solid carcinomas, 2 solid carcinomas with papillary areas, 1 interductal carcinoma and 4 that were unclassified.

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