Mammary Tumors Induced in Rats by Adriamycin and Daunomycin

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ABSTRACT
The two anthracycline antitumor antibiotics, Adriamycin and daunomycin (DM), induced a high incidence of mammary tumors, both fibroadenomas and adenocarcinomas, in female rats that received a single i.v. dose, thus confirming previous results. The incidence of DM-induced adenocarcinomas increased with the dose of the drug, whereas the incidence of Adriamycin-induced adenocarcinomas showed a plateau at 5 mg/kg and above. Adriamycin- and DM-induced fibroadenomas showed a peak at lower doses (about 5 to 6 mg/kg). With the highest DM dose (12.5 mg/kg) used, there was a slight prevalence of adenocarcinomas over fibroadenomas.

INTRODUCTION
In 1971 we reported a high incidence of mammary tumors in a relatively small group of rats treated with single doses of Adriamycin or DM, resulting in a sharp prevalence of fibroadenomas among Adriamycin-treated rats and adenocarcinomas among DM-treated rats (3). Recently, Marquardt et al. (4) confirmed the capacity of such antibiotics to induce mammary tumors in rats, but they failed to reproduce the preferential distribution of fibroadenomas and adenocarcinomas, which we had observed. We report here the results of a more extensive experiment with Adriamycin and DM given in a single i.v. injection at different doses.

MATERIALS AND METHODS
Adriamycin and DM were produced by Farmitalia, Milan, Italy. The drugs were dissolved in 0.9% NaCl solution (1 mg/1.25 ml). A total of 200 virgin female Sprague-Dawley rats (CD line; Charles River Breeding Laboratories, Calco, Italy), 2 months old, received a single injection of Adriamycin (4, 6.5, or 8 mg/kg i.v.; 100 animals) or DM (6.25 or 12.5 mg/kg i.v.; 100 animals). In preliminary experiments Adriamycin at doses of 10 and 12.5 mg/kg proved to be lethal and for this reason were not used in this study; 24 rats of the Adriamycin-treated group and 28 of the DM-treated group were found dead, in most cases before the surviving rats began to develop tumors. These animals were not included in the results. Kidneys, intestine, liver, and other organs were severely damaged in these animals (1, 2). The remaining 148 rats were killed when they showed palpable tumors or appeared debilitated, and the surviving animals were sacrificed 1 year after the injection. Fifty animals of the same strain and age were injected with 0.9% NaCl solution and served as controls. Of this control group, 10 were killed when they were found with tumor masses, 30 were killed 1 year after the injection, 3 were found dead, and the remaining 7 were killed 2 years after the injection. All animals were dissected, and the tissues were examined grossly. All tumor masses and abnormal viscera were examined microscopically. Tissue specimens were fixed with 4% formaldehyde + 0.5% calcium acetate, dehydrated in ethanol, and embedded in paraffin. Microtome sections were stained with hematoxylin and eosin.

RESULTS
Results on mammary tumors are shown in Table 1, Chart 1, and Figs. 1 and 2. Three extramammary tumors were also observed in the DM-treated group, including 2 s.c. fibrosarcomas and a thigh rhabdomyosarcoma. Only 1 control rat developed a tumor during the 12 months that followed the injection of 0.9% NaCl solution, whereas, of the 16 control rats that survived more than 12 months, 9 developed mammary tumors of which 7 were fibroadenomas and 2 were adenocarcinomas.

DISCUSSION
The above results confirm the capacity of single high doses of DM and Adriamycin to induce mammary tumors in female Sprague-Dawley rats. The incidence of such tumors in control rats was negligible until the end of the experiment.
Adriamycin, DM, and Mammary Tumors

Chart 1. Number of rats developing tumors (fibroadenomas or adenocarcinomas) during the 12 months after the injection of Adriamycin, DM, or 0.9% NaCl solution.

Chart 2. Percentage of rats developing tumors (fibroadenomas or adenocarcinomas) after treatment with Adriamycin or DM. The values for rats treated with 5 mg Adriamycin per kg and 5 or 10 mg DM per kg are from Marquardt et al. (4); the remaining data refer to the present study (see Table 1).

Fig. 1. Adriamycin-treated mammary tissue. Fibroadenoma. H & E, × 250.

Fig. 2. Daunomycin-treated mammary tissue. Adenocarcinoma. H & E, × 250.
when the animals were 14 months old; only 1 of 31 control rats developed a tumor during this time. However, the incidence of tumors was high in the next 12 months when 9 of 16 rats developed tumors. Thus, the anthracycline antibiotics studied seem to hasten greatly the development of mammary tumors in a strain of animals prone to the spontaneous development of the same tumor later in their life. In addition, the proportion of histologically malignant tumors appeared to be greatly increased in the treated rats.

The tumors of Adriamycin-treated rats were mostly fibroadenomas, whereas a slight preponderance of adenocarcinomas was found among DM-treated rats. These results confirm the results we obtained in a previous experiment (3), although at that time the preponderance of adenocarcinomas over fibroadenomas in DM-treated rats was clearer. Our results differ from those of Marquardt et al. (4) despite the fact that we used the same strain of rats and the same modality of treatment. As shown in Chart 2, the different doses of DM and Adriamycin used by the 2 groups may explain in part such discrepancies. It seems clear that the incidence of DM-induced adenocarcinomas increases in accordance with the drug dose, whereas Adriamycin-induced adenocarcinomas show a plateau at 5 mg/kg and above. Both Adriamycin- and DM-induced fibroadenomas show a peak at lower doses, whereas a preponderance of adenocarcinomas over fibroadenomas appears only with the highest DM dose (12.5 mg/kg). This dose had not been used by Marquardt et al. (4), although it was the only dose used in our previous experiment (3). Fibroadenomas are clearly prevalent over adenocarcinomas with all doses of Adriamycin and with DM at lower doses. The latter doses of DM were not used in our previous experiment (3), and this may explain the low incidence of fibroadenomas in the initial study.

These results confirm a high oncogenic potential of DM and Adriamycin. The ambivalence of antiblastic drugs has already been outlined (5). Thus far, tumors have been obtained only with single sublethal doses, which are much greater than those used in current therapeutic schedules. The oncogenic potential of lower and fractioned doses, a regimen similar to those used in cancer chemotherapy, is now being investigated extensively.

REFERENCES

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