Incidence of mammary tumours in rats during one year experiment

Treatment	Dose (mg/kg)	No. of rats	Rats dead during the experiment		Rats sacrificed at the end of the experiment		Total of tumour-bearing rats (A+B)	Tumour histology (A+B)	
			Without tumour	With tumour A	Without tumour	With tumour B		adenocarcinomas	fibroadenomas
Daunomycin	12.5	25	12	2	0	11	13	11	2
Adriamycin	8.–	25	17	1	1	6	7	1	6
Controls	–	25	0	0	25	0	0	0	0

observed 1 rabdomiosarcoma of the thigh and 1 polypus of the uterus; in the adriamycin group 1 meningioma and 2 uterine polypi were noticed. No tumours were found in the control animals. 14 of the 25 rats treated with daunomycin and 18 of the 25 rats treated with adriamycin died, due to severe renal damage or bone marrow aplasia, known to be induced by high doses of such antibiotics[8,10]. No relationship was found between death and presence or absence of tumours; in fact many rats died before tumour occurrence, particularly in the adriamycin group.

After 1 year of observation, all survivors and control rats were killed and examined carefully. Number of treated and control rats, doses, number of rats dead or sacrificed and breast-tumour incidence are plotted in the Table. In each tumour-bearing rat only 1 breast tumour and no metastases were found on extensive autoptic and histological examination.

Two findings are to be emphasized, i.e. the very high incidence of tumours in rats surviving until the end of the experiment, and the different histology of daunomycin tumours (mostly adenocarcinomas, Figure 1) in respect to adriamycin-ones (mostly fibroadenomas, Figure 2). The latter finding seems of high relevance, due to the close chemical similarity of the 2 antibiotics, which only differ in the presence of an hydroxy group linked to the C_{14}, present in adriamycin and absent in daunomycin.

Riassunto. La daunomicina (Daunorubicina) e l'adriamicina, antibiotici antitumorali, provocano dopo un'unica somministrazione endovenosa, nel ratto Sprague-Dawley di sesso femminile, l'insorgenza a distanza di alcuni mesi di tumori mammari, nel primo caso prevalentemente adenocarcinomi, nel secondo caso prevalentemente fibroadenomi.

C. BERTAZZOLI,[11] T. CHIELI[11] and E. SOLCIA[12]

Farmitalia, Istituto Ricerche, via dei Gracchi, 35, I-20146 Milano (Italy), and Istituto di Anatomia e Istologia Patologica dell'Università I-27100 Pavia (Italy), 25 January 1971.

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[11] Farmitalia, Istituto Ricerche, Via dei Gracchi 35, I-20146 Milano (Italia).
[12] Istituto di Anatomia e Istologia Patologica dell'Università, I-27100 Pavia (Italia).

Temporary Retardation of Cartilage Growth in Mice after External β-Irradiation[1]

Partial whole-body irradiation of mice with external ^{90}Sr-^{90}Y applicators may provide a way to control both the dose rate and time of exposure of skeletal tissues to β-rays. In this way, toxicity information can be obtained which is impossible to resolve by the use of internal emitters which deposit nonuniformly and are subject to a changing distribution with time owing to internal remodelling. This method has already been employed by BRUES et al.[2,3] to study skin carcinogenesis and the epidermal cell population kinectics in mice after irradiation with high doses at a slow rate (75 rads/h). We have examined the skeletons from some of these mice exposed to body surface doses of 5000 to 7200 rads, where the respective dose rates to the knee joint tissues and marrow were estimated to be of the order of 68 and 20–30 rads/h. The data indicate that cartilage growth was temporarily stunted after these high doses, but that recovery was able to occur.

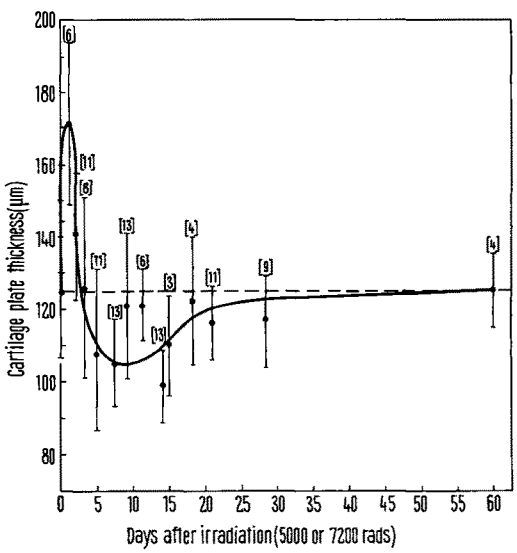
Materials and methods. The animals were drawn from 3 genetic strains of male C57 mice, black (C57 BL/6 ANL [ANL 66]), hairless white and haired analogues. At 4 months of age, they were exposed in a total-body surface β-irradiator (^{90}Sr-^{90}Y) designed by AUERBACH and BRUES[4]. The ^{90}Sr-^{90}Y source was in the form of ceramic microspherules embedded in polyurethane sheets. The sheet formed the inner lining of a 4″ long aluminum tube placed inside a wooden box, which was sealed by a 5/16″ thick fixed aluminum shield at one end and a similar but move-

able shield at the other. Irradiation was performed by inserting a mouse confined in a ventillated Lusteroid test tube within the source for 11 and 16 hours, but the head of the mouse was shielded from irradiation by a 1″ thick glass shield. Dosimetric studies using solid fluorod dosimeters in Lucite phantoms indicated a surface dose rate of 455 rads/h which decreased to 68 rads/h at a 3 mm depth well within the range of the surface tissues of the knee joint. The total body surface doses, then, for 11 h and 16 h irradiation periods were 5000 and 7200 rads, respectively. The maximum dose rate delivered to the cellular elements in the epiphyseal medullary cavities (about 5mm from the surface) might be expected to be on the order of 20–30 rads/h under optimal geometrical conditions. However, it was difficult to estimate the actual doses delivered to the knee joints. We do not know, for instance, if the knees were in contact with the walls of the Lusteroid tube during the entire 11 and 16 h exposure periods. A few control animals, both stressed (restrained in the test tubes) and unstressed were included in this preliminary study, but they were all sacrificed with the mice killed 1 day after irradiation to establish base line values. Other mice (2–4 in each strain) were sacrificed at various postirradiation times from 1–60 days.

The hind limbs of the mice were recovered at autopsy. They were fixed in 10% neutal formalin, decalcified in 10% EDTA, embedded in paraffin and sectioned longitudinally at 5 microns. The sections were stained with hematoxylin and eosin, and the thickness of the proximal tibial growth cartilage was measured with an ocular micrometer. The data for each postirradiation time has been averaged because the response to 5000 and 7200 rads was somewhat similar in all the mice and strain differences were not readily apparent.

Results and discussion. The histopathologic damage observed in the bones from the mice following partial whole-body irradiation involved cartilage, marrow and vascular anomalies similar to those previously described for rats[5,6] and mice[7]. These findings have been reported elsewhere[8]. We did not observe significant tissue disorganization other than a few instances of epiphyseal-diaphyseal union, but the thickness of the cartilages did vary at different postirradiation times. The Figure shows that on the first day, the cartilages became 25% thicker than normal, but thinned progressively from day 3–7. Thereafter, there was a brief period of recovery (days 9–13) which is possibly significant, followed by a second decline on day 14 and a return to normal by the end of the 3rd week. The standard error bars for each point on the graph are large, doubtless reflecting to some degree the genetic inhomogeneity of the mice.

Because the pace of endochondral ossification in 4-month-old mice is generally very slow, we believe that the changes in the cartilage were due mainly to an effect of irradiation upon cell division and matrix synthesis. We did not observe postirradiation recovery clones of cells in the cartilages as did SAMS[7] and KEMBER[9,10], although in mice these are relatively late effects to acute X-irradiation (9 weeks after 2000 R). The bones of older mice also seem generally less responsive to irradiation probably because there are fewer replicative cells at risk[6]. In the present study, we suspect that both age and the low dose rate of beta irradiation influenced the mild response in the cartilages. In common with KEMBER's[11] experience, the curve for cartilage thickness shows a pattern of recovery suggesting adaptation to irradiation. It resembles, particularly, the pattern of metaphyseal bone cell recovery in young rats following acute exposure to X-irradiation and single injections of ^{32}P where the cell dose was as in this experiment equal to or somewhat greater than 300 rads.



A plot of the thickness of the growth cartilage of mice versus the number of days after partial-whole body β-irradiation with ^{90}Sr-^{90}Y external applicators. The horizontal bars represent the standard errors of the means. Numerals enclosed in parentheses indicate the number of mice/group. The dotted line shows the thickness of the cartilage in unirradiated control mice.

Résumé. Sur les cartilages de conjugaison de souris adulte, on a mesuré par une méthode histologique l'effet de grandes doses de rayonnements béta de ^{90}Sr-^{90}Y appliquées à 68 rads/h pendants 11–16 h. Après l'irradiation, les changements d'épaisseur du cartilage ont suggeré un modèle de dommages et de récupération qui ressembla à une réponse adaptive aux expositions unique de l'X-irradiation.

D. J. SIMMONS[12], R. HAKIM[13] and H. CUMMINS[12]

Radiological Physics Division,
Argonne National Laboratory,
Argonne (Illinois 60439, USA), and 114 Oxford Street,
Cambridge (Massachusetts 02139, USA),
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[12] Radiological Physics Division, Argonne National Laboratory, Argonne (Illinois 60439, USA).
[13] 114 Oxford Street, Cambridge (Massachusetts 02139, USA).