Protection Against Cocarcinogenesis by Antioxidants

The metabolic sequence of events responsible for the initiation and promoting stages of co-carcinogenesis has not been elucidated.

The reactions of the co-carcinogens with skin components may produce free radicals or peroxidize lipid membranes. A hydroperoxide derived from cholesterol has been shown to be carcinogenic under certain conditions[1]. The main reaction of polycyclic hydrocarbons appears to be oxidation by hydrogen peroxide or an oxygen atom to activate double bonds, to yield intermediary epoxides[2].

Peroxidation may damage cells in several ways[3]: destruction of enzymes and cytochromes of electron transport; destruction of cytochrome b_5; breaking of lysosomal and microsomal lipid membranes and releasing of hydrolytic enzymes; and hemolysis of erythrocytes.

In this preliminary study, mice were first initiated with 7,12-dimethylbenzanthracene. Antioxidants and free radical inhibitors were applied concomitantly with the tumor promoter, i.e. croton oil.

30 ICR Swiss female mice, 55–60 days old, were initiated once with 125 γ 7,12-dimethylbenzanthracene dissolved in 0.25 ml acetone. After a period of three weeks, the animals were painted five times weekly for 16 weeks with 0.25 ml of a mixture of 0.033% croton oil and the various test substances dissolved in an 80% acetone, 20% water solution. The test substances were 0.0005% sodium selenide, 0.01% hydrocortisone, 0.25% D,L-α-tocopherol and 0.25% cysteamide. The group which received the croton oil alone was the positive control. One group received 7,12-dimethylbenzanthracene only. The animals were examined weekly and the number and distribution of tumors were noted. Results after 16 weeks are indicated in the Table.

Sodium selenide applied concomitantly with the croton oil markedly reduced tumor formation (Table). Selenium is a known powerful antioxidant[3]. Hydrocortisone and D,L-α-tocopherol also reduced tumor formation. Both substances protect against lipid peroxidation[5,6]. Cysteamide, known to protect against radiation[7], had a small protective effect. The relative effectiveness of each antioxidant was calculated (Table). Sodium selenide was 2780/3.78 or 735 times as effective as D,L-α-tocopherol against tumor formation. Selenium antioxidants on a molar basis are known to have 500 to 2000 times the antioxidant activity of D,L-α-tocopherol in vitro[3].

Antioxidants are likely to inhibit early critical oxidation and reduction reactions necessary for tumor formation[8].

The effect of antioxidants on the prevention of croton oil induced tumors

0.033% croton oil + addition	No. of tumors	Relative effectiveness[4]
Sodium selenide	9	2780.0
D,L-α-Tocopherol acetate	50	3.8
Hydrocortisone	55	65.8
Cysteamide	84	0.37
None	132	0
Dmba only	0	–

Zusammenfassung. Natrium-Selenid und andere Antioxydantien können die Entstehung von Tumoren hemmen. Die Wirkung kommt möglicherweise zustande über eine Hemmung der Bildung von Co-Carcinogenen.

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The Effect of Splenectomy on the Radiation Disease of in utero Irradiated Foetus

If the spleen is removed per laparotomiam within 5 h after a sublethal whole-body irradiation, the survival rate of mice and rats is higher than in the case of animals which were sham operated or only irradiated[1,2]. It is assumed that in the irradiated spleen a humoral factor is formed which influences the radiation disease unfavourably. The liberation of this factor seems to be prevented by splenectomy[3]. This assumption is supported by the limited time of effectiveness of splenectomy[1] and the higher survival rate of splenectomized mice[4]. While opinions substantially agree that the shielded spleen or injected spleen cells[5–7] have a protective effect, it has not yet been clarified why the irradiated spleen blocks bone-marrow regeneration. Both the formation of a humoral factor[8,9] and the destruction of protective or resistance factors[10] in the irradiated spleen are possible causes.

The question of the extent to which splenectomy is able to modify radiation damage of the foetus will now be examined. From the 12th to the 17th day of pregnancy[11], 6 groups of 15 mice each were subjected to whole-body irradiation with 250 R. 2 h after irradiation, 5 mice were splenectomized, 5 were sham operated and 5 were anaesthetized in each group. The rate of deceased and resorbed foetus was calculated on the 20th day of pregnancy after section.

The Table shows that splenectomy within 2 h after whole-body irradiation with 250 R results in no improvement of foetal survival rate. On the contrary, the foetal death rate is higher in the case of splenectomized and

The survival rate and the average weight of the foetus after 250 R whole-body irradiation performed 2 h previous to splenectomy and sham operation dependent on the day of pregnancy

Day of pregnancy	Survival rate	Average weight	Survival rate	Average weight	Survival rate	Average weight
	250 R without operation		250 R 2 h before sham operation		250 R 2 h before splenectomy	
17th day	100.0%	1.41 ± 0.12 g	95.0%	1.36 ± 0.14 g	100.0%	1.33 ± 0.14 g
16th day	100.0%	1.34 ± 0.13 g	76.0%	1.27 ± 0.13 g	81.7%	1.21 ± 0.13 g
15th day	90.5%	1.29 ± 0.13 g	39.0%	1.25 ± 0.13 g	32.9%	1.15 ± 0.12 g
14th day	60.0%	1.16 ± 0.14 g	5.9%	0.98 ± 0.11 g	9.5%	0.99 ± 0.12 g
13th day	32.6%	1.06 ± 0.12 g	0.0%	0.90 ± 0.10 g	0.0%	0.81 ± 0.10 g
12th day	0.0%	0.98 ± 0.11 g	0.0%	0.84 ± 0.11 g	0.0%	0.88 ± 0.11 g

sham-operated mice than for irradiated mice. Damage as a result of operation shock must therefore be assumed.

No definite conclusion as to the diffusibility of the spleen factor can thus be made from the inability of splenectomy to increase the foetal survival rate. Analogous to the 'recovery factor' in non-irradiated spleen[12], however, it can be assumed that there is the question of a diaplacentally non-diffusible macromolecule[13].

Zusammenfassung. Eine Splenektomie 2 h nach einer Ganzkörperbestrahlung von 250 R führt bei graviden Muttertieren zu keiner Verbesserung der fötalen Überlebensrate. In Analogie zum 'recovery factor' der gesunden Milz darf angenommen werden, dass sich in der bestrahlten Milz ein hochmolekularer, diaplazentar nicht diffusionsfähiger Stoff bildet.

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Effect of Selenium on Food and Water Intake in the Rat

Epidemiological studies among children and work with experimental animals, reviewed recently[1], have shown that selenium increases the susceptibility to caries when consumed during the period of the development of the teeth and incorporated into their structure. On the other hand, administration of selenium to rats after the development of their teeth did not increase caries[2,3]. However, in these experiments the animals on selenium showed evidence of toxicity including retardation of growth which is one of the main symptoms of selenium poisoning resulting from lack of appetite and food intake. Since food intake in rodents is directly related to the development of caries, the present experiment was designed to test the effect of selenium ingestion on both the food and water intake in rats. No such study has been reported previously.

Materials and methods. Thirty male weanling Sprague-Dawly strain rats weighing between 43–50 g were equally divided into a selenium and a control group. The animals were housed individually in metal cages with raised screen bottoms. Selenium, as sodium selenite, in the amount of 3.0 ppm was added to the drinking water of the experimental group and offered ad libitum. It has been shown that, in general, water does not contain appreciable amounts of selenium[4]. The controls were drinking tap water. All animals were fed ground Purina laboratory chow ad libitum. The food was placed in scatter-proof food cups, made of metal, with a cover having a central feeding hole of $1^1/_4$ in. diameter. The water consumption was measured accurately by using non-spillable animal drinking tubes, made of glass, having a capacity of 100 ml, and graduated at intervals of 1 ml. The amount of food consumed daily was measured by a double beam balance. The experiment lasted for 4 weeks and during that period two animals in the experimental group died from selenium poisoning.

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