supported by the preliminary report that homozygous CPK mice have serum corticosterone levels which are eight times higher than those of age-matched controls[12].
This finding is of particular importance in light of the proven cyst-inducing effects of various glucocorticoids[10,11,13,14]. Studies are currently underway to further define the environmental factors which may promote, as well as prevent, the development of genetically programmed cystic tubular changes in the CPK model.

Acknowledgments. These studies were supported by Basil O'Connor Starter Research Grant 5-349 from the March of Dimes Birth Defects Foundation and New Investigator Research Award AM34891 from the National Institutes of Health (both to EDA).

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0014-4754/86/010077-04$1.50 + 0.20/0

Teratogenic interactions between cadmium and radiation in mice

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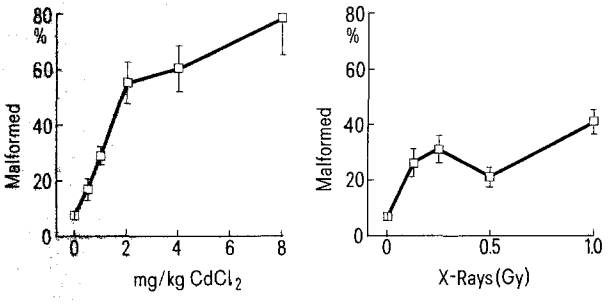
Summary. Mouse embryos were exposed to various doses of cadmium and/or X-rays on day 8 of gestation. The combined treatment exerted an antagonistic effect regarding the teratogenic action of the two agents.
Key words. Embryonic development; mice; teratogenic interaction; cadmium; X-irradiation.

The contamination of the environment with heavy metals, and their potential toxicity, have received increasing interest. Concern about health effects of cadmium mainly relates to the carcinogenic, teratogenic and mutagenic action of this metal. So far, there is no conclusive evidence that cadmium produces these effects in humans[1,2].
Regarding cadmium-induced embryotoxicity, animal experiments demonstrate a broad spectrum of developmental anomalies, depending on dose, gestational age, application and genetic factors[3–8]. It is evident that several chemicals and environmental factors modify the teratogenicity of heavy metals[9]. There are indications that additive or synergistic relationships exist between in vivo application of Cd^{2+} and radiation[10]. Experiments in vitro with preimplantation mouse embryos revealed an additive behavior of the two agents[11].
In our previous studies, the combined treatment of mouse embryos with radiation and drugs has shown various degrees of potentiation[12,13]. The objectives of the present work are to determine the embryotoxic effects of cadmium and possible interactions in vivo with X-rays during a highly sensitive stage of development in mice.
Materials and methods. Virgin female NMRI-mice, aged 10–12 weeks, were mated overnight and examined for a copulation plug the next morning (day 0 of gestation). On day 8, pregnant animals were whole-body exposed to 0.125, 0.25, 0.5, and 1.0 Gy of 200 kV X-rays (12 mA, 1 mm Al + 0.5 mm Cu filtration, 1. HVL = 0.93 mm Cu, dose rate 0.465 Gy/min). Five groups of mice were injected i.p. with $CdCl_2$ on day 8 (0.5–8.0 mg/kg b.wt). Control animals were injected with 1 ml of physiological saline. In combined treatment 2 mg/kg $CdCl_2$ was injected 30 or 60 min before or immediately after irradiation. The experiments were made in series of replicates, each with a group of 5–8 females. On day 13 of gestation the fetal mortality, growth retardation and malformations were evaluated. The data were analyzed using the Mann-Whitney ranking test.
Results. Concerning teratogenic effects of cadmium, a linear dose-effect curve was found up to the dose of 2 mg/kg (fig.). Qualitatively, microphthalmia dominated at lower Cd doses whereas high frequencies of exencephaly occurred with doses of 2 and more mg/kg. At the highest dose (8 mg/kg), 55% of the implantations were dead, i.e. embryolethality prevails over the induction of malformations. Up to 4 mg $CdCl_2$/kg the fetal mortality rates varied between 6% and 9.4% compared to 10% in the control (NaCl) group ($p > 0.05$).
The dose effect relationship for radiation-induced teratogenicity between 0.125 and 1.0 Gy is not linear (fig.). In qualitative respects, exposure to 1 Gy resulted in a significant increase of exencephaly compared to lower doses (table). No increase in the rates of lethality and growth retardation were observed in the irradiation groups in comparison to control mice.
So far, combined application of cadmium (2 mg/kg) and 0.5 or 1.0 Gy has been tested (table). The most interesting finding is the reduced rate of malformations in the co-insult experiments when Cd was applied 30 or 60 min before irradiation. The antagonistic relation in the teratogenic activity was less pronounced when cadmium was given 60 min before 0.5 Gy. The decreased general malformation rate is mainly due to the generally lower incidence of exencephaly (8% and 16% compared to 35% in the Cd



Teratogenic effects of cadmium alone (left) and X-rays alone in 13-day-old mouse fetuses after treatment on day 8 of gestation.

Survival, growth retardation and malformations after treatment with $CdCl_2$ and/or radiation on day 8 of gestation. Examination on day 13. Only statistically significant differences are entered

Treatment $CdCl_2$ (mg/kg)	Radiation (Gy)	No. of litters	Live fetuses No. (%)[a]	Growth retardation No. (%)[b]	Malformations Total No. (%)[b]	Exencephaly	Eye	Others
–	–	33	413 (90.0)	38 (9.2)	45 (10.9)	0.5%	6.3%	4.1%
2.0	–	14	190 (92.7)	18 (9.5)	104 (54.7)[c]	35.8%[c]	18.4%[c]	0.5%
–	0.5	25	287 (90.5)	21 (7.3)	67 (19.9)[c]	1.5%	15.0%[c]	3.8%
2.0[e]	0.5	18	238 (90.5)	40 (16.8)	54 (22.7)[d]	8.0%[d]	12.6%	2.1%
2.0[f]	0.5	16	180 (90.0)	11 (6.1)	86 (48.0)	22.2%	23.5%	2.2%
–	1.0	24	266 (90.8)	29 (10.9)	110 (41.4)[c]	12.0%[c]	25.9%[c]	3.4%
2.0[e]	1.0	17	219 (95.2)	33 (10.5)	98 (44.7)	16.4%	27.3%	1.0%
2.0[g]	1.0	14	134 (81.2)	18 (13.4)	92 (68.7)	18.7%	50.0%	–

[a]Percentage of implantations; [b]percentage of live fetuses; [c]$p < 0.02$ compared to NaCl-control; [d]$p < 0.02$ compared to $CdCl_2$ alone; [e]30 min before irradiation; [f]60 min before radiation; [g]immediately after irradiation.

treated group). The proportion of microphthalmia and anophthalmia also reached a subadditive level except when $CdCl_2$ was administered immediately after X-irradiation. In this case a synergistic relation exists between the two agents involved. Among the other malformations mainly tail defects, one spina bifida (Cd plus 1.0 Gy) and one duplicitas posterior (Cd plus 0.5 Gy) were observed. It may be noted that combinations of cadmium and radiation showed no significant interaction concerning lethal or growth retarding effects.

Discussion. These results confirm the teratogenic activity of cadmium in animal experiments exerting a significant increase in the rate of exencephaly and eye anomalies. Exposure of mouse embryos to a single dose of 0.5 or 1.0 Gy X-rays resulted mainly in microphthalmia, as the only type of eye malformation. Coadministration of the heavy metal with X-rays on day 8 of gestation in mice resulted in a interesting antagonism of teratogenesis. It is evident that the frequency of exencephaly, a severe defect of the central nervous system, is smaller in all combined treated groups than in the corresponding Cd-group. The antagonistic effect of radiation and cadmium was generally most pronounced when the time interval between the application of the two agents was 30 min. This finding suggests that the specificity of the teratogenic interaction is time-dependent, and may explain the varying degrees of antagonism in brain and eye damage. Concerning the induction of eye malformations the antagonistic action of cadmium with irradiation was less pronounced compared to that of exencephaly. In one case, where $CdCl_2$ was given immediately after 1.0 Gy, even a supra-additive response with respect to the development of eye damage has been found. This synergism may be explained by the absence of an adequate protection mechanism against the disturbance of the eye morphogenesis.

Protection against the teratogenic action of cadmium was also achieved with zinc, selenium, mercury and pretreatment with cadmium[9]. It is postulated that this protective effect may be due to the induction of maternal synthesis of metallothionein[14]. This protein binds cadmium and may prevent the embryotoxic effects during sensitive stages of development. This hypothesis and further possible explanations for the observed antagonism are the subject for our future work.

Acknowledgments. This research was supported by the Swiss National Foundation for Scientific Research, grant Nr. 3.126-0.81.

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0014-4754/86/010080-02$1.50 + 0.20/0

Ontogenetic changes in isozyme patterns during seed germination of self-pollinated *Secale* species[1]

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Summary. Six isozymatic systems have been studied comparatively during the first week of germination of seeds of self-pollinated *Secale* species (*S. silvestre* Host. and *S. vavilovii* Gross.). Isozymatic systems do not change at all, or reach their definitive adult plant pattern early during germination.
Key words. Secale silvestre; *Secale vavilovii*; isozyme changes; seed; germination.

The expression and/or the activity level of particular isozymes, and sometimes all the isozymes of an isozymatic system, are often related to a tissue, an organ or a developmental stage[2,3]. Differences in isozymatic patterns among different tissues and organs, or during development, have been attributed to one or more of the following causes: 1) changes in the level of isozyme expression; 2) genetic transcription of different isozyme loci; and, 3) post-translational isozyme modifications changing the electrophoretic mobility. Many examples of organ specificity, or changes during development, or isozyme patterns have been reported in higher plants, including cereals. For the latter there are several reports, for example of organ specificity in *Triticum*[4] and *Secale*[5,6], and of changes during development[7-9]. On the other hand, the expression of different isozyme loci at different developmental stages or in different organs, and changes in electrophoretic mobility which facilitate the isozyme resolution