

BRIEF COMMUNICATION

EFFECT OF CADMIUM CHLORIDE ON THE  
PREGNANT ALBINO MOUSE

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The selective and destructive action of a single subcutaneous injection of cadmium chloride on the testes of various laboratory animals was first described by Pařízek in 1956 (see Pařízek, 1957). These observations have been confirmed and extended in a number of laboratories (Cameron & Foster, 1963; Chiquoine, 1964; Gunn, Gould & Anderson, 1961, 1963; Kar & Das, 1960; Mason, Brown, Young & Nesbit, 1964; Meek, 1959; Pařízek, 1957). On the other hand, no effect of such an injection on the female reproductive system was noted (Gunn *et al.*, 1961; Pařízek, 1960). Recently Pařízek (1964) has reported that a single subcutaneous injection of 0.04 mM CdCl<sub>2</sub>/kg body weight given to pregnant rats on the 17th to 21st day of pregnancy resulted in destruction of the foetal portion of the placenta and death of the embryos.

The study reported here documents the sensitivity of the pregnant albino mouse to cadmium chloride and provides a timetable for the development of this sensitivity. The findings also indicate that the effect of cadmium on the female reproductive tract is not one of permanent damage and that the animal can be protected against the action of cadmium chloride by a previous priming with zinc acetate.

A random-bred colony of Swiss albino mice was used to obtain timed pregnancies. Females were placed with males in the evening and checked for a vaginal plug on the following morning. The morning of finding a vaginal plug is considered Day 0 and in this particular colony pregnant females consistently litter on Day 19. Over the course of several months, females of known days of pregnancy were given a single subcutaneous injection of 0.1 mg in 0.1 ml of CdCl<sub>2</sub>/10 g body weight (0.02 mM/kg) either between the scapulae or over the rump. All injections were given at 09.00 hours and the animal was then set aside and observed for subsequent parturition or was killed 24 hr after the injection. From the latter, appropriate tissues were fixed in Bouin's fluid and prepared for microscopic study.

*Action of cadmium chloride*

Of a total of twenty-five females receiving an injection of cadmium chloride on any day of pregnancy from the 6th to 17th day none maintained pregnancy to a normal parturition. It is possible that some of the animals receiving the injection prior to the 12th day of pregnancy, at which time pregnancy is

grossly obvious, were indeed not pregnant but microscopic study of an additional ten females (see below) confirmed the destructive action of cadmium on embryo and uteri.

Animals injected on the 14th, 15th, 16th or 17th day of pregnancy and killed 24 hr later showed gross signs of necrosis. Haemorrhages within the uterus were visible to the eye and the fact that the embryos were dead was ascertained by the absence of movement and of a functioning foetal circulation. Similar gross signs of alteration of the uterine vascular system were seen in earlier ages and microscopic sections of implantation sites from the 6th to the 12th day of pregnancy revealed embryos showing varying degrees of autolysis and disintegration. Thus it may be concluded that a single injection of cadmium chloride given to pregnant mice on any day from the 6th to the 17th day of pregnancy results in intra-uterine death of the embryos and localized necrosis of the placenta or adjacent decidual tissue.

To test the action of cadmium on embryonic stages before and during implantation, pregnant mice were given a single injection of the standard dose on Days 1, 2, 3, 4 or 5 and then set aside for the remaining period of gestation. For each day, at least three pregnant animals were injected and for each of these days of pregnancy at least one animal littered; the actual figures, in daily order, being two out of three, three out of three, two out of three, three out of three, and one out of five for Day 5. It would appear therefore that sensitivity to cadmium on the part of the female reproductive tract commences at about the time of implantation, i.e. Day 5.

The control experiments to the above consisted of pregnant animals injected with saline or with an equivalent amount of mercuric chloride (0.1 ml of 0.1%  $\text{HgCl}_2$ /10 g body weight). All saline-injected control animals littered normally. Animals injected with mercuric chloride prior to Day 15 of pregnancy also littered normally, but two of the four animals injected on Day 16 and 17 died a few hours after the injection. The kidneys of these animals, perhaps damaged by mercuric ions, showed a grey discoloration suggesting that the animals died from uraemia.

It would appear that although such injections of cadmium bring about an extremely rapid placental necrosis and foetal death, no irrevocable harm has been done to the maternal organism. Five pregnant females on the 14th day of pregnancy, when pregnancy is grossly visible, were given a single injection of cadmium and all failed to litter. However, after a 2-week isolation period, these same females were again housed with a male and subsequently littered and raised their young normally.

#### *Action of zinc acetate*

Another five females obviously pregnant were given two injections of 0.1 ml of 10% zinc acetate (2 mm/kg), on the 14th day of pregnancy, 12 and 7 hr before the injection of cadmium. One of these mice died during the next 8 hr; the other four littered on schedule and raised their young. These findings, therefore, document the similarity in the action of cadmium on the testis and pregnant uterus. In both instances the animal can be protected against the action of cadmium by previous injections of zinc.

In documenting the sensitivity of the pregnant mouse to 0.02 mM/kg of cadmium ion, this study is consistent with the findings of Pařízek (1964) that the pregnant rat is sensitive to 0.04 mM/kg. However Maekawa & Hosoyama (1965) failed to find any effect on pregnancy in rats given 1.5 mg of cadmium chloride on the 14th, 16th or 18th day of pregnancy. The reason for this discrepancy is not known at this time.

Pařízek (1964) suggested as a hypothesis that cadmium produces selective circulatory damage in oestrogen-producing organs, e.g. the testis, the ovary and the placenta, but for the present there is no positive evidence to support this hypothesis. Although oestrogen has been extracted from the testes of some animals (such as the stallion, bull, deer and man—see Albert, 1961) the fact that the testes of mice or rats also synthesize oestrogen is by no means documented. Similarly, oestrogen has been extracted from or shown to be synthesized by tissue slices of the placentas of a variety of species but this is not true of rat (Huggett & Hammond, 1952). It is also pertinent to this point that the pregnant mouse has been shown in this study to be sensitive to cadmium prior to the time of formation of a placenta on the part of the embryo. A review of the literature on the action of cadmium on the reproductive organs can only lead to the conclusion that the phenomenon is in the process of being clearly documented, particularly by the investigations of Pařízek, but that the actual mechanism of action of cadmium ions is very much of an open question.

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