TOXIC ACTION OF CARBON DISULFIDE ON REPRODUCTIVE FUNCTION AND POTENTIATION OF THE EFFECT BY TRYPTOPHAN

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Chronic poisoning of albino mice and rats was produced by daily inhalation of carbon disulfide in a concentration of 2000 mg/m^3 throughout the period of pregnancy. Carbon disulfide did not affect the duration of pregnancy or the weight of the albino rat fetuses, but it had an embryotoxic action, causing death of the embryos at all stages of intrauterine development. Administration of tryptophan potentiated the action of carbon disulfide. No anomalies or malformations of the fetuses were found.

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A few cases have been reported which show the effects of occupational hazards on intrauterine development of the fetus and on the newborn infant. Experimental studies of several toxic substances used in industry have shown that most of them possess high teratogenic activity. So far, however, there is no experimental evidence of the effect of carbon disulfide on the course of pregnancy and parturition or on the intrauterine development of the fetuses.

The object of this investigation was to study the action of carbon disulfide on reproductive function, and to reduce the risk of errors. Two species of animals with a hemochorial type of placenta were used.

EXPERIMENTAL METHOD

Experiments were carried out on albino mice (weight 22-26 g) and Wistar rats (weight 150-120 g). Throughout pregnancy the animals inhaled carbon disulfide in a concentration of 2000 mg/m^3 for 2 h daily. Half the mice were poisoned for the two weeks before mating, and some mice from this group received tryptophan in a dose of 500 mg/kg from the 1st until the 19th-20th day of pregnancy.

Some animals produced their young spontaneously, while fetuses were extracted from the others on the 19th-20th day of pregnancy. The number of corpora lutea in the ovaries and of implantation sites in the uterus was counted. The preimplantation mortality was calculated (in %) as the difference between the number of corpora lutea and the number of implantation sites expressed as a ratio of the number of corpora lutea. The postimplantation mortality was determined in percent from the number of implanted embryos.

EXPERIMENTAL RESULTS

In the experiments of series I the course and duration of pregnancy were studied in the albino rats. The mean duration of pregnancy in the experimental rats was 22.2 ± 0.6 days compared with 23.2 ± 0.2 days in the control ($0.25 > P > 0.05$).

The results of these investigation (Table 1) indicate no significant differences between the number of corpora lutea in the females of the two groups, which may be indirect evidence of the homogeneous com-

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TABLE 1. Embryonic Mortality Among Albino Rats After Carbon Disulfide Poisoning (series I)

Group of animals	No. of animals	No. of corpora lutea	No. of embryos dying before implantation	Total no. of implanted embryos	No. of embryos dying after implantation	No. of living fetuses	
						abs.	in % of number of corpora lutea
Experimental	12	107	18(16,8%)	89	7	82	76,6
		8,9±0,6	1,5±0,3	7,4±0,7	0,6±0,7	6,8±0,7	$_2$76,6±4,4
		120		116		116	96,9
Control	12	10,0±0,6	4(3,3%)	9,7±0,7	—	9,7±0,7	$_2$96,9±1,1
		$P>0,05$		$P<0,05$		$P<0,05$	

Note. Numerator gives total number of animals in group, denominator index for one animal.

TABLE 2. Embryonic Mortality among Albino Rats after Carbon Disulfide Poisoning (series II)

Group of animals	Number of animals	Number of corpora lutea	No of embryos dying before implantation	Total no. of implanted embryos	No. of embryos dying after implantation	No. of living fetuses	
						abs.	in percent of number of of corpora lutea
experimental	12	124	28	96	—	96	77,4
		10,3±0,7	2,3±0,4	8,0±0,8		8,0±0,8	77,4±6,6
control	14	139	9	130		130	93.5
		9,9±0,5	0,6±0,2	9,3±0,8	—	9,3±0,8	93,5±2,4
		$P>0,05$	$P<0,05$				$P<0,05$

position of the compared groups of animals. Only 83.2% of fertilized ova were implanted in the experimental rats, compared with 96.7% in the control group. The mean number of implantation sites per rat poisoned with carbon disulfide was less than in the control group; this difference is statistically significant (Table 1; $P < 0.05$). The preimplantation mortality among the experimental animals was 5 times higher (16.8%) than in the controls, indicating that carbon disulfide has a marked toxic action on the developing fetus during the period of early embryogenesis. The results also indicate that postimplantation mortality was observed only in animals poisoned with carbon disulfide. In the control group, death of the embryos was not found after implantation. The fertility of the animals differed in the two groups: the mean number of embryos per rat in the experimental group was 6.8 ± 0.7, and 9.7 ± 0.7 in the control. This indicates lower fertility among females poisoned with carbon disulfide. To determine the effect of carbon disulfide on intrauterine development of albino rat fetuses, the mean weight of the fetus was calculated. No retardation of development of the embryos was found among the rats of the experimental group (mean weight of fetus 5.9 ± 0.1 g; control 5.9 ± 0.5 g).

In the experiments of series II (Table 2), no mortality among the fetuses was observed in the postimplantation stage of development; all implanted embryos were alive. Fertility was higher than in the control group of animals. The preimplantation mortality was found to be 3 times greater among the experimental animals than among the controls. Data for embryotoxic action of carbon disulfide on albino mice are given in Table 3. The absence of significant differences in the number of corpora lutea between the control mice and those poisoned with carbon disulfide before mating suggest that the compound does not affect the fertilizing ability of mice. The preimplantation mortality among the control animals was 11.2%, and 18.7% in the experimental mice. The differences are statistically significant ($P < 0.05$), thus again confirming the hypothesis that embryos are more sensitive to carbon disulfide in the preimplantation period of development. The total number of implanted embryos in the poisoned animals was less than in the controls (81.3% compared with 89.8; $P < 0.05$). The fact that death of the embryos was observed after implantation only in the mice of the experimental group deserves note. Dead embryos were found in 7.4% of cases. This indicates that carbon disulfide possesses embryotoxic properties and disturbs intrauterine development of the fetuses in both pre- and postimplantation periods. The fertility of mice poisoned with carbon disulfide was also significantly lower than that of the controls ($P < 0.05$).

TABLE 3. Effect of Carbon Disulfide and Tryptophan on Embryonic Mortality of Albino Mice

Group of animals	Number of animals	Number of corpora lutea	No. of embryos dying before implantation	Total number of implanted embryos	Number of embryos dying after implantation	Number of living fetuses
Control	21	204 9,7±0,3	23 1,1±0,06	181 8,6±0,3	—	181 8,6±0,3
Experimental (carbon disulfide)	15	133 8,9±0,5 >0,05	25 1,7±0,2 <0,001	108 7,2±0,5 <0,05	8	100 6,6±0,52 <0,05
Experimental (carbon disulfide + tryptophan	20	177 8,9±0,36 >0,05	49 2,5±0,2 <0,05	128 6,4±0,4 <0,05	3	125 6,3±0,3 <0,05
Experimental (tryptophan)	20	190 9,5±0,3 >0,05	24 1,2±0,06 >0,05	166 8,3±0,2 >0,05	5	161 8,1±0,42 >0,05

An important role in the pathogenesis of carbon disulfide poisoning is played by blocking of monoamine oxidase, an enzyme essential for the biotransformation of serotonin, by dithiocarbamino compounds (carbon disulfide metabolites) of the catalytic centers. Poisoning with carbon disulfide leads to an increase in the serotonin concentration in the brain and blood of animals [2]. The embryotoxic action of carbon disulfide is considered to be associated with excessive accumulation of serotonin. Numerous investigations have shown that serotonin, when injected into animals, causes death of fetuses and the interruption of pregnancy [3], and the taratogenic properties of serotonin have been described [4]. To confirm the role of accumulation of serotonin in the embryotoxic action of carbon disulfide, experiments were carried out on albino mice to which the serotonin precursor, tryptophan, which increases serotonin formation in the body [5], was administered during pregnancy. The embryonic mortality after the combined action of carbon disulfide and tryptophan was much higher in the animals of the experimental group than in the controls (Table 3). For instance, the preimplantation mortality in these animals was 2.5 times higher than in the control mice (27.6% compared with 11.2%).

LITERATURE CITED

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