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Cocaine as a Cause of Congenital Malformations of Vascular Origin: Experimental Evidence in the Rat

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ABSTRACT Cocaine hydrochloride was administered to pregnant Sprague-Dawley rats as a single intraperitoneal dose or as two doses 1–4 hours apart. A single dose administered on day 16 of gestation was teratogenic in a dose-dependent manner, with 40 mg/kg being a no-effect dose and 50 mg/kg the lowest teratogenic dose; 80 mg/kg was lethal to the dam. Forty-eight hours after exposure to a teratogenic dose on day 16 of pregnancy, the fetuses showed severe hemorrhage and edema in the their extremities, particularly the footplates, tail, genital tubercle, and upper lip/nose. When the fetuses were examined on day 21 of gestation, the main externally visible malformations were reduction deformities of the limbs and tail. When two doses of cocaine were administered 1–4 hours apart, the incidence of affected fetuses increased as the time interval between the two doses decreased. Two doses of cocaine administered 2 hours apart were not teratogenic on day 9, 10, 11, 12, 13, or 14 of gestation but did induce reduction deformities on days 15, 16, 17, 18, or 19. The same dose administered 1 hour apart was teratogenic on days 14–19. In general, cocaine administration on gestational days 14, 15, or 16 induced more severe and more widespread hemorrhage and edema than administration on days 17, 18, or 19. In the latter cases, damage was restricted to the distal parts of the hindlimb digits and the tail. The results show that in the rat cocaine is only teratogenic during the late organogenic or postorganogenic period. It exerts its teratogenic effect by inducing hemorrhage and edema in the fetuses, which lead to necrosis and disruption of existing and developing structures, particularly the limbs. It is proposed that cocaine causes severe constriction of the uterine vasculature, leading to an hypoxic response in the placental/fetal unit, which causes the observed hemorrhage and edema.

There is considerable clinical evidence that cocaine abuse during pregnancy is associated with a high rate of spontaneous abortion, abruptio placentae, prematurity, low birth weight for gestational age, and neurobehavioral deficiencies in some neonates (Chasnoff et al., '85; MacGregor et al., '87; Bingol et al., '87). A small number of congenital malformations have also been reported, including prune belly syndrome, ileal atresia, hypospadias, and limb malformation (Chasnoff et al., '88; Hoyme et al., '88; Chavez et al., '88). The limb malformations consisted of the absence of digits 3 and 4 of the left hand (Fig. 1) and were seen in two children. This is a very unusual malformation, but it is similar to limb defects seen in rat fetuses from dams exposed to various forms of uterine trauma, including uterine vessel clamping, late in pregnancy (Webster et al., '87). It was proposed that these defects were due to a vascular response in the fetus as a consequence of hypoxia caused by the marked reduction in uterine blood flow. Because cocaine is known to be a potent vasoconstrictor and has been shown to cause a profound decrease in uterine blood flow in

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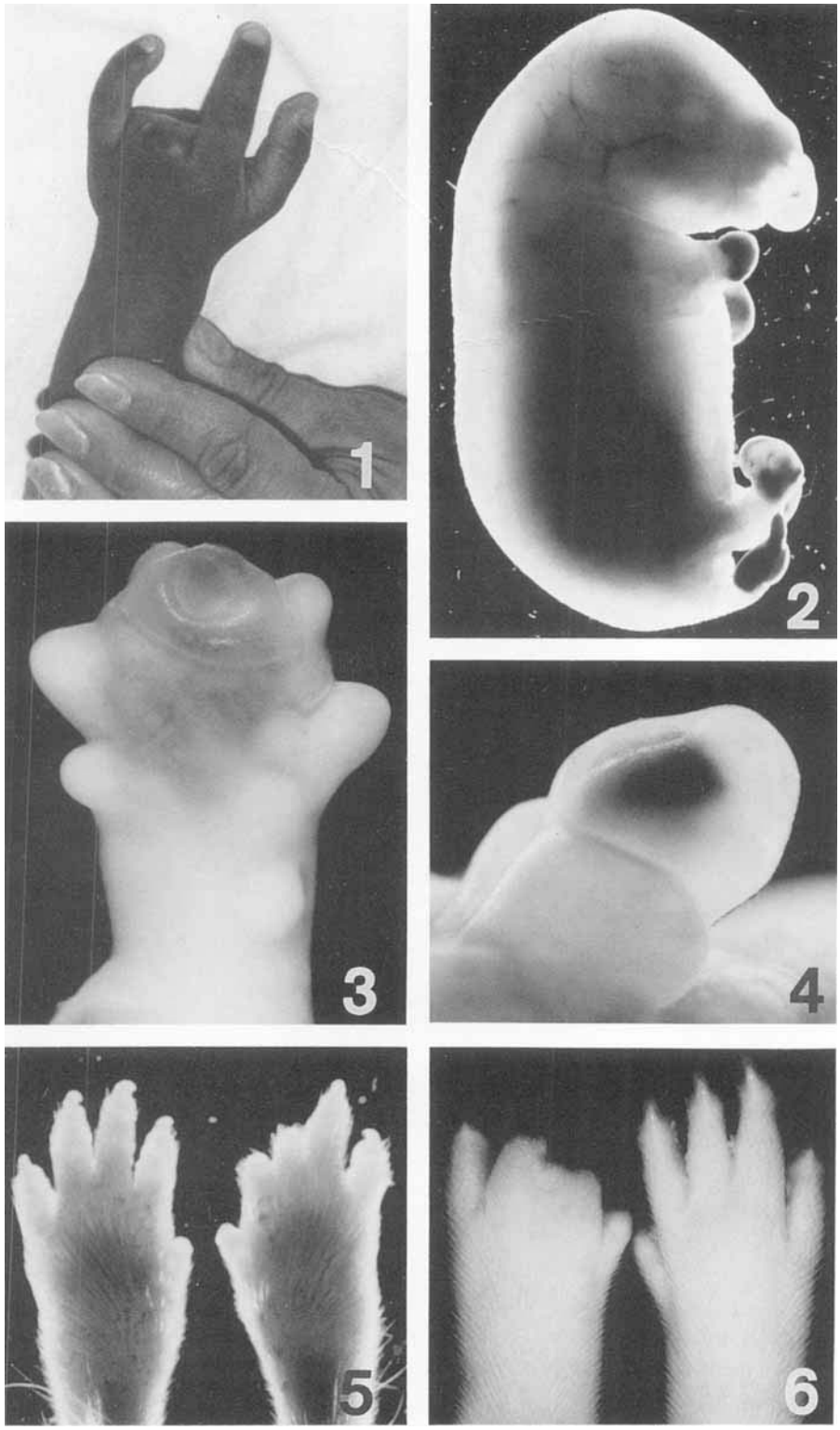


Figs. 1–6.

the pregnant ewe (Woods et al., '87), we suspected that the teratogenic effects of cocaine may be related to our previous observations in the rat. The hypothesis was that cocaine abuse at a similar stage of gestation, namely during the late organogenic or postorganogenic period, would cause severe constriction of the uterine blood vessels, which in turn would cause a vascular response in the fetal-placental unit and subsequent hemorrhage in the fetus, particularly in extremities such as the digits, tail, upper lip/nose, and genital tubercle.

In the present study, cocaine was administered to pregnant rats as single or multiple doses, and the fetuses were examined at various times postinjection for evidence of hemorrhage and malformation. This work has previously been reported in abstract form (Webster et al., 1989).

MATERIALS AND METHODS

Sprague-Dawley rats were mated overnight and examined the next morning by vaginal smear. Rats with a sperm-positive smear were separated, and this day was considered day 0 of gestation.

Dose-response study

Previous studies had indicated that uterine vascular clamping on day 16 of gestation caused severe fetal hemorrhage; so the initial dosing studies were performed on day 16 of gestation. Rats were lightly anesthetized with ether and given a single intraperitoneal (i.p.) injection of cocaine hydrochloride (Glaxo Australia Pty. Ltd.) freshly dissolved in distilled water (200 mg/10 ml) at a dose of 40, 50, 60, 70, or 80 mg/kg body weight. Control rats received an injection of distilled water equivalent in volume to the 60 mg/kg dose. The rats were killed 48 hours later by carbon dioxide inhalation, and the fetuses were carefully removed and weighed and then examined for external malformations and cleft palate using a dissecting microscope. To investigate the time period during which hemorrhages occurred, some rats were given a 60 mg/kg cocaine dose and killed 1, 2, 4, or 8 hours after dosing, and the fetuses were examined using a dissecting microscope.

Treatment interval study

Rats on day 16 of gestation were given two i.p. injections of cocaine hydrochloride (50 mg/kg) at intervals of 1, 2, 3, or 4 hours. The rats were killed 48 hours later and the fetuses weighed and examined. Controls received two injections, 1 hour apart, of distilled water equivalent in volume to the 60 mg/kg dose.

Stage of pregnancy study

Pregnant rats were given two i.p. injections of cocaine hydrochloride (50 mg/kg) 2 hours apart on day 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 of gestation. All rats were killed on day 21 of gestation, and the fetuses were weighed and examined. An additional group of rats were given two i.p. injections (50 mg/kg) 1 hour apart on either day 13, 14, 15, 16, 17, 18, or 19 of gestation. These rats were killed either 48 hours later or on day 21 of gestation. Control rats received two injections, 1 or 2 hours apart, of distilled water equivalent in volume to the 50 mg/kg dose.

Statistics

For statistical analysis, the litter was considered to be the experimental unit, and the percentages of abnormal fetuses and resorptions between control and experimental animals were compared by Mann-Whitney U-test. Fetal weights were compared using analysis of variance.

Fig. 1. Left hand of an infant born to a mother described as a heavy cocaine user (Chasnoff et al., '88). Note the absence of the 3rd and 4th digits. (Photo courtesy of Dr. I. Chasnoff, Department of Pediatrics, Northwestern Memorial Hospital, Chicago, Illinois 60611).

Fig. 2. Rat fetus from a dam given a single dose of cocaine (60 mg/kg) 48 hours earlier. Note the severe hemorrhage affecting the footplates and tail and the large fluid-filled blister on the nose and upper lip.

Fig. 3. Palmer surface of the forelimb of a rat fetus from a dam given cocaine (60 mg/kg) 48 hours earlier on day 16. Note the large blood-filled blister affecting the 2nd, 3rd, and 4th digits.

Fig. 4. Genital tubercle of an 18-day rat fetus from a dam given cocaine (60 mg/kg) 48 hours earlier. There is a large hemorrhage in the tubercle.

Fig. 5. Left and right forelimbs of 5-week rat from a dam given cocaine (60 mg/kg) on day 16 of gestation. Note the reduction of 2nd and 3rd digits of right limb.

Fig. 6. Right and left hindlimbs of 5-week rat from a dam given cocaine (60 mg/kg) on day 16 of gestation. Note the reduction of digits 2–4 of the left limb.

TABLE 1. Effect of dose on cocaine teratogenesis on embryonic day 16 in the rat (fetuses examined 48 hours later)

Treatment (mg/kg)	No. of rats	No. of litters	Mean litter size	Percent of implants resorbed	Percent of live fetuses abnormal	No. of affected litters	Mean fetal weight (g)
40	5	5	17.2	1.1	0.0	0/5	1.23 ± 0.06*
50	7	7	14.0	5.0	7.3*	3/7	1.29 ± 0.08
60	6	5	16.0	3.4	21.5*	4/5	1.27 ± 0.16*
70	5	2	11.0	18.7*	45.8*	2/2	1.24 ± 0.09
80	4	0					
Controls	5	5	12.8	0.0	0.0	0/5	1.41 ± 0.10

*Significantly different from the control; $P < 0.05$.

RESULTS

Cocaine administration on day 16 of gestation induced severe hemorrhages in the fetuses primarily affecting the footplates and tail (Figs. 2–4). Hemorrhages were first visible in the fetuses 2 hours after dosing and continued to be evident for up to 96 hours. For most experiments, the fetuses were examined 48 hours after cocaine dosing, and it is possible that some of the small hemorrhages had disappeared by that time. For example, 4 hours after dosing, many fetuses showed scattered subcutaneous hemorrhages, but similar hemorrhages were rarely seen after 48 hours. When the fetuses were examined 5 days after dosing, there were reduction deformities of the limbs and tail corresponding to the most common sites of hemorrhage. A few rats were allowed to litter after receiving cocaine on day 16 of gestation; many of the offspring survived with permanent defects of the forelimbs and hindlimbs (Figs. 5, 6).

Cocaine was teratogenic in a dose-dependent manner over a very narrow dose range (Table 1). Doubling the no-effect level (40 mg/kg) produced a maternally lethal dose (80 mg/kg). The teratogenic dose range (50–70 mg/kg) induced hemorrhage and sometimes edema in fetuses examined 48 hours after dosing. The hemorrhages were often severe, affecting the entire footplate of both forelimbs and hindlimbs, the distal part of the tail, the genital tubercle, and sometimes the upper lip and adjacent part of the nose (Fig. 2). Less severe damage was restricted to the distal parts of the middle digits of the limb and the distal part of the tail. Fetal weight for all treatment groups was reduced compared with controls (Table 1), and the resorption rate was significantly increased in the 70 mg/kg group.

The possible synergistic effect of two doses of cocaine was investigated using the marginally teratogenic dose of 50 mg/kg (Table 2). A single injection of this dose caused hemorrhage in about 7% of the fetuses. When two doses were given 1 hour apart, the number of affected fetuses increased to 29.5%, two doses 2 hours apart affected 23%, and two doses 3 hours apart affected 17%. Surprisingly, two doses 4 hours apart did not result in as many affected fetuses as the single dose, although the number of resorptions was increased.

In general, hemorrhages and edema were more severe following the higher doses of cocaine or when two doses were administered 1 hour apart. Damage to the upper lip/nose, genital tubercle (Fig. 4) and whole body edema were also associated with the higher doses.

Preliminary studies had shown that two doses of cocaine (50 mg/kg) administered 2 hours apart on day 16 of gestation caused significant hemorrhage in surviving fetuses 48 hours later without causing maternal death. On the basis of these results, this dosage was selected to investigate the effect of the stage of pregnancy on cocaine teratogenicity. Regardless of the day of treatment, the fetuses were examined on day 21 of gestation. The results of this study (Table 3) show that this dose induced a low incidence of externally visible malformations, and these were restricted to litters dosed on days 15–19. All of the malformations were reduction defects of the limbs and tail. The administered dose was particularly embryotoxic or fetotoxic on gestational days 9 and 17–19, and on treatment days 10 and 11 the dose was lethal to most of the dams. One of the control fetuses showed reduction deformities of the middle digits of both hindlimbs as well as forelimb syndactyly and microphthalmia.

TABLE 2. Effect of treatment interval on cocaine teratogenesis in the rat on embryonic day 16 (fetuses examined 48 hours later)

Dose (50 mg/kg)	No. of rats	No. of litters	Mean litter size	Percent of implants resorbed	Percent of live fetuses abnormal	No. of affected litters	Mean fetal weight (g)
1 injection	7	7	14.0	5.0	7.3	3/7	1.29 ± 0.08
2×1 hr	5	5	13.4	12.0*	29.5*	4/5	1.30 ± 0.09
2×2 hr	7	5	12.8	17.5*	23.1*	4/5	1.20 ± 0.19
2×3 hr	5	5	13.0	13.3	17.0	3/5	1.16 ± 0.12*
2×4 hr	5	4	11.0	13.1	1.8	1/4	1.30 ± 0.02
Controls	4	4	14.3	1.5	0.0	0/4	1.33 ± 0.02

*Significantly different from control; $P<0.05$.

TABLE 3. Effect of stage of pregnancy on cocaine teratogenesis in the rat (2 i.p. doses 50 mg/kg 2 hours apart, killed on day 21)

Day of treatment	No. of rats	No. of litters	Mean litter size	Percent of implants resorbed	Percent of live fetuses abnormal	No. of affected litters	Mean fetal weight (g)
9	4	3	9.0	35.4	0.0	0/3	4.90 ± 0.79
10	6	1	18.0	0.0	0.0	0/1	4.34
11	4	1	15.0	0.0	0.0	0/1	4.58
12	3	3	14.3	0.0	0.0	0/3	4.53 ± 0.16
13	3	2	14.0	0.0	0.0	0/2	4.62 ± 0.16
14	3	3	10.7	6.3	0.0	0/3	5.20 ± 0.39*
15	4	4	15.0	0.0	7.8	1/4	4.31 ± 0.13
16	4	3	15.7	5.7	4.2	1/3	4.51 ± 0.41
17	5	4	11.8	17.3*	4.5	1/4	4.55 ± 0.16
18	5	4	12.3	9.9*	7.3	3/4	4.43 ± 0.66
19	5	2	3.0	12.5	16.7	1/2	5.13 ± 0.28
Controls	6	6	13.0	0.9	1.1	1/6	4.46 ± 0.79

*Significantly different from the control; $P<0.05$.

The relatively low incidence of affected fetuses led to a subsequent experiment in which the two doses were administered 1 hour apart and the fetuses examined either 48 hours later (Table 4) or on day 21 of gestation (Table 5). Malformations were restricted to treatment days 14–17; and in most instances the dose resulted in a marked increase in the number of affected fetuses. Again, one of the control fetuses was abnormal, having a reduced fourth digit on the left forelimb, reduced middle digit on the left hindlimb, and cleft palate.

The overall relationships between dose, day of treatment, and location of hemorrhage, edema, or abnormality are presented in Table 6. For gestational days 14–19 inclusive, cocaine exposure on any single day damaged the fetal limbs. Forelimb defects were restricted to treatment days 14–17; hindlimb defects were most numerous after exposure on days 16 and 17 and were the only limb defects on days 18 and 19.

Cocaine exposure late in gestation (days 17–19) caused hemorrhage only in the distal parts of the footplate (Fig. 7), whereas exposure on earlier days (14–16) led to a much greater variation in damage ranging from involvement of the entire footplate (Fig. 8) to minor hemorrhage leading to loss of the distal part of the middle digit (Fig. 9). The tail was affected at all treatment times. Hemorrhage in the genital tubercle was associated with cocaine exposure on days 15, 16, or 17. The most common abnormalities of the head region were hemorrhages in the middle of the upper lip and adjacent part of the nose seen in litters treated on days 15, 16, and 17. Other less frequently seen head malformations included hemorrhages in the eye, cerebral hemispheres, and mandible. Whole-body edema was associated with the higher teratogenic doses of cocaine.

Not included in the total of abnormal fetuses are 12 fetuses that showed abdominal hemorrhage 48 hours after cocaine exposure on day 16. These 12 fetuses occurred in 11 litters, and only two of the fetuses showed other evidence of hemorrhage or edema. Dissection of the fetuses revealed that there was severe hemorrhage in the liver and in the apices of the lungs.

TABLE 4. Effect of stage of pregnancy on cocaine teratogenesis in the rat (2 i.p. doses 50 mg/kg 1 hour apart, killed 48 hours later)

Day of treatment	No. of rats	No. of litters	Mean litter size	Percent of implants resorbed	Percent of live fetuses abnormal	No. of affected litters
13	6	3	14.3	4.6	0.0	0/3
14	4	4	13.5	21.2*	27.0*	3/4
15	5	4	12.3	10.7	54.3*	4/4
16	5	5	13.4	9.9	29.5	4/5
Controls	4	4	14.3	1.5	0.0	0/4

*Significantly different from the control; $P<0.05$.

TABLE 5. Effect of stage of pregnancy on cocaine teratogenesis in the rat (2 i.p. doses 50 mg/kg 1 hour apart, killed on day 21)

Day of treatment	No. of rats	No. of litters	Mean litter size	Percent of implants resorbed	Percent of live fetuses abnormal	No. of affected litters	Mean fetal weight (g)
13	5	3	14.0	6.3	0.0	0/4	4.22
14	5	4	10.8	26.9	15.5	3/4	4.71 ± 0.46
15	4	4	13.3	0.0	66.1	3/4	4.43 ± 0.43
16	6	6	11.8	11.8	16.0*	5/6	4.71 ± 0.29
17	7	3	15.3	6.0	11.0*	3/3	4.43 ± 0.08
18	5	1	11.0	8.3	0.0	0/1	4.88
19	1	1	9.0	18.2	0.0	0/1	4.76
Controls	5	5	12.8	1.5	1.6	1/5	4.70 ± 0.43

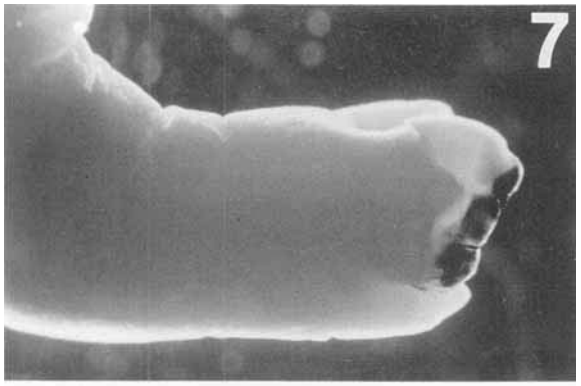
*Significantly different from the control; $P<0.05$.

TABLE 6. Relationships between dose of cocaine, day of treatment and location of abnormality in rat fetuses

Day treatment/ sacrifice	Dose (mg/kg)	No. of doses	No. of fetuses abnormal/ normal	Forelimbs (%)	Hindlimbs (%)	Tail (%)	Genital tubercle %	Head %	Edema %
16/18	50	1	6/98	67 (4/6)	83 (5/6)	33 (2/6)	50 (3/6)	33 (2/6)	
16/18	60	1	18/80	56 (10/18)	72 (13/18)	66 (12/18)	22 (4/18)		
16/18	70	1	10/22	90 (9/10)	90 (9/10)	90 (9/10)	30 (3/10)	30 (3/10)	30 (3/10)
16/18	50	2 (1 hr apart)	19/67	32 (6/19)	47 (9/19)	53 (10/19)	5 (1/19)	21 (4/19)	16 (3/19)
16/18	50	2 (2 hr apart)	14/64	79 (11/14)	93 (13/14)	86 (12/14)	29 (4/14)	29 (4/14)	14 (2/14)
16/18	50	2 (3 hr apart)	9/65	67 (6/9)	89 (8/9)	44 (4/9)			
16/18	50	2 (4 hr apart)	1/44	100 (1/1)	100 (1/1)	100 (1/1)	100 (1/1)		
15/21	50	2 (2 hr apart)	5/60			100 (5/5)			
16/21	50	2 (2 hr apart)	2/47		50 (1/2)	50 (1/2)			
17/21	50	2 (2 hr apart)	2/47		100 (2/2)		50 (1/2)		
18/21	50	2 (2 hr apart)	4/49		25 (1/4)	75 (3/4)			
19/21	50	2 (2 hr apart)	1/6		100 (1/1)				
16/21	0	2 (2 hr apart)	1/78	100 (1/1)	100 (1/1)			100 (1/1)	
14/16	50	2 (1 hr apart)	15/54	40 (6/15)		40 (6/15)		40 (6/15)	13 (2/15)
15/17	50	2 (1 hr apart)	24/49	29 (7/24)		92 (22/24)	17 (4/24)	38 (9/24)	4 (1/24)
16/18	50	2 (1 hr apart)	17/55	35 (6/17)	47 (8/17)	53 (9/17)	6 (1/17)	18 (3/17)	18 (3/17)
14/21	50	2 (1 hr apart)	9/43	22 (2/9)	89 (8/9)			22 (2/9)	
15/21	50	2 (1 hr apart)	35/53	66 (23/35)	31 (11/35)	89 (31/53)			
16/21	50	2 (1 hr apart)	11/71	73 (8/11)	91 (10/11)	82 (9/11)			
17/21	50	2 (1 hr apart)	5/46	40 (2/5)	60 (3/5)	80 (4/5)			
16/21	0	2 (1 hr apart)	1/64	100 (1/1)	100 (1/1)			100 (1/1)	

DISCUSSION

The possibility that cocaine is a human teratogen is based on a prospective study of 50 women who conceived while addicted to cocaine and who were still actively using cocaine when they enrolled in the study during the first trimester of pregnancy (Chasnoff et al., '88). Nine of the 50 offspring had congenital malformations. Two had ileal atresia and seven had a malformation of the



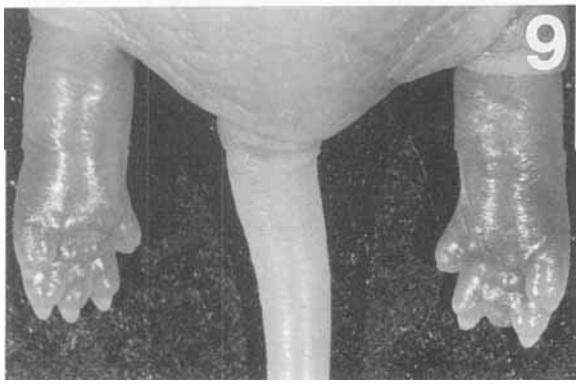


Fig. 7. Right hindlimb of a 21-day fetus from a dam given cocaine (2 × 50 mg/kg 1 hour apart) on day 17 of gestation. There is hemorrhage in the distal parts of digits 2–4.

Fig. 8. Right and left hindlimbs of a 21-day fetus from a dam given cocaine (2 × 50 mg/kg 1 hour apart) on day 16 of gestation. The footplates of both hindlimbs are missing, and there is eschar formation on the limbs and tail.

Fig. 9. Right and left hindlimbs of a 21-day fetus from a dam given cocaine (2 × 50 mg/kg 1 hour apart) on day 14 of gestation. Note the reduction of the 3rd digit of the left hindlimb.

genitourinary tract. Two of these latter children had isolated second-degree hypospadias and three had hydronephrosis. The other two infants had multiple congenital malformations, described as prune belly syndrome; both had hydronephrosis, absence of the 3rd and 4th digits of the left hand, and abnormalities of the genitalia. One of these infants, a male, also had second-degree hypospadias with chordee and undescended testes; the other infant, a female, had ambiguous genitalia with absent uterus and ovaries, deficient abdominal musculature, anal atresia, and unilateral talipes equinovarus. The same investigators (Chasnoff et al., '85) had previously associated prune belly syndrome and hypospadias with cocaine abuse during pregnancy. There have also been two abstracts describing similar malformations in the offspring of cocaine users (Chavez et al., '88; Hoyme et al., '88); included in one of these studies (Hoyme et al., '88) were six children with limb anomalies.

In another study of 50 women, prenatal cocaine use was retrospectively associated with five major congenital malformations (Bingol et al., '87), including one case of exencephaly, one parietal encephalocele, one parietal bone defect, and two heart defects. This latter study was criticized for failure to control for variables such as polydrug, alcohol and cigarette use, and possible poor nutritional status (Bauchner et al., '87).

As indicated by Brent ('85), part of the proof of teratogenicity of a substance should involve the development of an animal model at the "therapeutic" pharmacokinetic exposure to which the human is exposed. For cocaine, previous studies have been not been particularly positive. In one study, mice were given a single subcutaneous injection of cocaine hydrochloride (60 mg/kg) on day 7, 8, 9, 10, 11, or 12 of gestation, and the fetuses were examined on day 18 of gestation (Mahalik et al., '80). A low incidence of exencephaly, cryptorchidism, hydronephrosis, anophthalmia, and malformed or missing lenses as well as delayed ossification and malformed sternebrae and xiphoid processes was reported. The malformations were induced over a wide range of treatment days (exencephaly days 7–10, cryptochidism days 7–12, hydronephrosis 7–12, anophthalmia 7–12) as were the bony anomalies. Many of the treated fetuses showed delayed ossification, suggesting that the

cryptochidism and hydronephrosis might be related to immaturity rather than being true malformations. The authors did not state how they defined hydronephrosis, as may be necessary in such cases (e.g., Taylor, '86). In the second study, rats and mice were given daily doses of cocaine during the organogenic period (Fantel and Macphail, '82). The rats were given i.p. injections of 50, 60, or 75 mg/kg cocaine hydrochloride on days 8–12 of gestation inclusive, and the fetuses were examined on day 20 of gestation. The mice were given i.p. injections of 60 mg/kg on days 7–16 inclusive, and the fetuses were examined on day 18 of gestation. Despite the extensive treatment periods, there was no increase in congenital malformations. The rats showed significant reductions in maternal and fetal weights as well as increased resorption frequencies and fetal edema. The mice showed decreased fetal weights but no increase in malformations. The third study involved rats given a daily subcutaneous injection of cocaine hydrochloride (40, 50, 60, 70, 80, or 90 mg/kg) starting on day 7 of gestation and continuing until day 19 (Church et al., '88). Each daily dose was split evenly, with the first portion administered in the morning and the second in the afternoon. The fetuses were examined on day 20 of gestation. The higher doses were associated with extensive maternal death. Abruptio placentae (as evidenced by vaginal bleeding and retroplacental clots) was seen in four litters of the higher-dose groups. Fetal edema was seen in 23 fetuses from six litters, and hemorrhagic areas were seen in 23 fetuses from ten litters exclusive of those fetuses with edema. The majority of the hemorrhages were in the cephalic region. Two physical anomalies were observed in the 360 fetuses: unilateral anophthalmia and microcephaly.

The results of the present study show that cocaine is teratogenic in a dose-dependent manner when administered during the late or postorganogenic period in the rat. There was no evidence of teratogenicity during the main organogenic period even when cocaine was administered at maternally toxic levels; this confirms the previous studies of Fantel and MacPhail ('82) and Church et al. ('88) using the rat. A possible explanation for this observed period of sensitivity is that the fetal vasculature has to reach a certain degree of maturation before it can respond to hypoxia.

The malformations induced by cocaine are unusual because they are preceded by hemorrhage and edema in developed and developing structures. Subsequent necrosis, disruption, and amputation leads to a range of reduction deformities of vascular origin. Limb malformations were the most prominent defect in the rat, and amputation or reduction of the middle digit correlates well with the two limb defects described in the human (Chasnoff et al., '85). Internal and histological examination of the fetuses was not done; so we have no information on other malformations such as hypospadias, hydronephrosis, prune belly syndrome, and ileal atresia, which have been associated with cocaine use during pregnancy. The presence of hemorrhage in the liver and lungs of some fetuses suggests that damage to the viscera may occur by a similar mechanism to the limb defects. Similarly, hemorrhage was frequently seen in the genital tubercle, but it has not been established whether or not this can lead to hypospadias or obstruct the flow of urine to cause hydronephrosis or prune belly.

In view of the repetitive nature of cocaine use in the human, we examined whether two doses of cocaine would have a synergistic effect. A clear potentiation was seen, but it may be due to an overlap of cocaine serum levels resulting in the fetal/placental unit being exposed to higher concentrations of the drug.

In conclusion, it is proposed that cocaine is a teratogen that can cause fetal abnormality by disrupting previously established structures. In this respect, the abnormalities seen in the present study could be called disruptions rather than malformations . Its teratogenic effect is most likely to occur in the postorganogenic period, although there is some evidence of an earlier effect on neural tube closure (Mahalik et al., '80; Bingol et al., '87). The proposed pathogenesis for its postorganogenic effect is that the cocaine causes vasoconstriction of the uterine vessels as has been shown to occur in the pregnant ewe at blood cocaine levels known to occur in the human (Moore et al., '86; Woods et al., '87). The uterine blood vessels are normally maximally dilated operating at or near maximum hemodynamic efficiency, and resting adrenergic tonus in the uterine vascular bed of the gravid ewe is minimal (Greiss and Gobble, '67). Cocaine blocks the reuptake of norepinephrine at nerve end-

ings, resulting in increased circulating levels of this catecholamine (Moore et al., '86), which then may lead to stimulation of the uterine blood vessels. Such stimulation can lead to profound uterine vasoconstriction almost to the point of entirely compromising uterine blood flow (Greiss and Gobble, '67). Previous studies in the rat (Leist and Grauwiler, '74; Webster et al., '87) have shown that such reduction in uterine blood flow leads to a hypoxic response in the fetal-placental unit, which causes edema and hemorrhage in the fetus. Subsequent tissue damage can lead to a range of disruption-type malformations (Leist and Grauwiler, '74; Webster et al., '87), the most obvious of which are amputation or hypoplasia of the digits. Although there is good evidence that cocaine can cross the placenta (Shah et al., '80), studies in the ewe have indicated that maternally administered cocaine causes a greater cardiovascular response in the fetus than does cocaine injected directly into the fetus (Woods et al., '87). These data support the uterine vascular hypothesis as the etiology.

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