Prenatal and Neonatal Exposure to Cimetidine Results in Gonadal and Sexual Dysfunction in Adult Males

Abstract. *Exposure of rats to cimetidine during intrauterine life and the immediate neonatal period results in hypoandrogenization in adult life with decreased weights of androgen-dependent tissues and decreased concentrations of testosterone. Moreover, sexual behavior patterns in adult life are disturbed as shown by a lack of sexual motivation and decreased performance.*

Cimetidine is used extensively in the treatment of acid peptic disease (*1*). In addition to being an H_2 receptor antagonist, cimetidine is a well-documented antiandrogen. Its mechanism of antiandrogenic action is related to its ability to compete with testosterone for cytosolic androgen receptors at target tissues, thereby reducing specific nuclear uptake of the sex steroid by these organs (*2*).

Of special importance to the study described herein is that cimetidine freely crosses the placental barrier during gestation and is excreted into breast milk. Cimetidine in breast milk actually reaches concentrations several times greater than those in the serum when measured simultaneously (*3*).

Testosterone subserves several critical functions during intrauterine life and the immediate neonatal period (*4*). Its presence is responsible for male sex organ differentiation and the sexual differentiation or imprinting of the fetal brain. An androgen-imprinted brain is associated in adult life with masculine patterns of hormonal release and masculine patterns of sexual behavior (*5*). In this study we administered cimetidine to female rats during pregnancy and lactation and examined the antiandrogenic effects of the drug on gonadal development, gonadal function, and sexual behavior patterns in the male progeny.

Pregnant dams (Wistar) received cimetidine mixed in their drinking water (intake 137 ± 49 mg/kg-day) from day 12 of gestation through the birth of the pups to the time of weaning (21 days after birth). The male progeny of these treated dams were assessed for gonadal development, structure, and function, as well as sexual function and signs of masculinization. These data were compared to those for the male progeny of untreated control dams. The anogenital index, a measure of masculinization, was determined during the period of exposure to the drug via the breast milk. All other parameters, consisting of sex organ weights and histologic structure, concentrations of serum testosterone, and studies of male sexual behavior, were obtained after the pups were fully mature adult rats.

Anogenital distances (defined as the distance from the anterior edge of the anal opening to the base of the phallus in the male and to the urethra in the female) were measured at days 1 and 5 after birth by means of a dissecting microscope and micrometer eyepiece (Olympus G 10X) (*6*). This distance was then corrected for body weight and expressed as an index. Normally, the anogenital index in the male is approximately twice that in normal females. All pups were weaned from their mothers at 21 days of age and housed in colony cages (two to three per cage). Testicles, seminal vesicles, and prostate glands were weighed at 55 days of age (puberty normally appearing at 40 to 45 days of age) on a Mettler Pc 440 balance that we read to the nearest 0.01 g. Testicles were weighed after decapsulation; prostate glands and seminal vesicles were weighed as a unit. Serum testosterone was determined at 55 days of age by radioimmunoassay according to the method of Neichslag and Loriaux (*7*). Blood samples were obtained either by retroorbital puncture with microhemato-

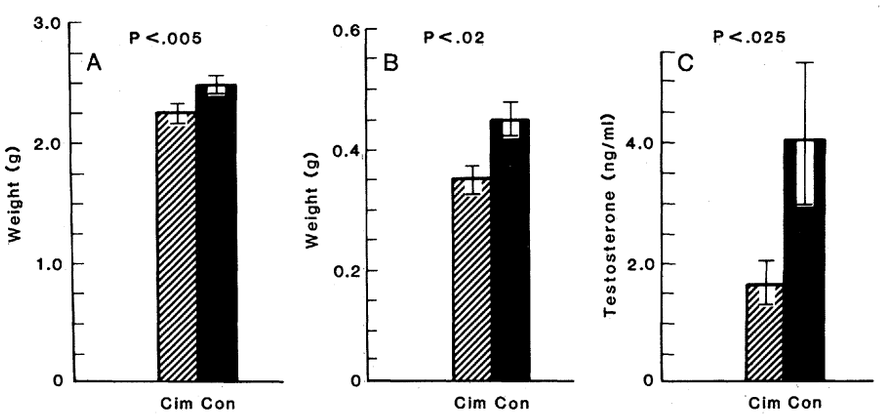

Fig. 1. Evidence for hypoandrogenization in cimetidine-exposed animals (*Cim*, cimetidine; *Con*, control). (A) Testicular weight. (B) Prostatic and seminal vesicle weight. (C) Testosterone concentration in serum. All data are for animals at 55 days of age. Bars represent mean values (N = 10) and brackets represent the standard error.

Table 1. Evidence for lack of masculinization in cimetidine-exposed animals; N.S., not significant.

Group	Neonatal life						Adult life mounting patterns at 110 days	
	Day 1 after birth			Day 5 after birth				
	Anogenital distance (mm)	Body weight (g)	Anogenital index	Anogenital distance (mm)	Body weight (g)	Anogenital index	Mount latency (seconds)	Number of mounts in 15 seconds
Cimetidine-exposed	19 ± 0.46 N = 11	7.42 ± 0.1 N = 11	2.6 ± 0.03 N = 11	29 ± 1.13 N = 24	11.7 ± 0.6 N = 24	2.56 ± 0.05 N = 24	375 ± 172 N = 6	4 ± 2 N = 6
Control	21 ± 0.14 N = 12	6.5 ± 0.09 N = 12	3.2 ± 0.04 N = 12	32 ± 0.7 N = 22	10.4 ± 0.2 N = 22	3.06 ± 0.05 N = 22	31 ± 13 N = 6	15 ± 2 N = 6
P	< .005	< .01	< .005	< .025	N.S.	< .005	< .05	< .05

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crit tubes (Sherwood) or by aortic puncture.

Sexual behavior patterns were determined at 110 days of age. A receptive female primed with exogenous estradiol and progesterone was placed in the company of a cimetidine-exposed male in a test arena to which the male had been allowed to adapt for 5 minutes. Mounting patterns (latency period and the number of mounts) in a 15-minute period were recorded. The latency period was the time elapsed after introduction of the receptive female to the first mount by the test male. The performance of each cimetidine-exposed male was compared with that of a control male with the same female, to exclude possible differences in female receptivity. We used the Student's *t*-test (two-tailed) for all statistical analyses, considering a P value of $< .05$ as significant.

Anogenital distances and indices were reduced significantly in the cimetidine-exposed rats on day 1 and on day 5 compared to the controls (Table 1). Weights of the testicles and of the prostate glands and seminal vesicles at 55 days of age were reduced in the cimetidine-exposed animals compared to the controls (Fig. 1). Examination of testicular histology by light microscopy revealed no differences between the two groups. Compared to the control animals, the rats exposed to cimetidine showed reduced serum testosterone (Fig. 1), prolonged mount latency periods, and fewer mounts.

The reduced anogenital distances and indices in the cimetidine-exposed animals indicate a lack of masculinization at a period of exposure to cimetidine through breast milk. The reduction in sex organ weights at 55 days of age suggests a long-lasting specific antiandrogenic effect resulting in subnormal growth of androgen-responsive tissues even after discontinuation of the drug (35 days earlier). It may be that intrauterine and neonatal exposure to cimetidine modifies end-organ androgen receptor activity or responsiveness in either a qualitative or quantitative manner, rendering these organs less sensitive to androgenic stimulation later in life.

The reduction in testosterone concentrations in the cimetidine-exposed group cannot be fully explained by the present data. A long-lasting direct inhibitory effect of cimetidine on the hypothalamic-pituitary-gonadal axis is possible, making this axis relatively insensitive to negative feedback by testosterone. Deficient androgen imprinting of the fetal brain during intrauterine and neonatal life, as a consequence of intrauterine and neonatal exposure to cimetidine, may have resulted in a lack of sexual motivation in the adult animal. It should be noted that in addition to decreased sexual motivation, a decrease of sexual performance also occurred in the cimetidine-exposed animals compared to the controls.

On the basis of these results in rats, and until the controversy regarding the role of sex steroid imprinting of the human fetal brain has been settled, we suggest that cimetidine should be used with caution in pregnant humans, especially during possible critical periods for neuroendocrine programming of the fetal brain.

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DDT in the Sewers

Fry and Toone (*1*) stated that "Between 1950 and 1970 offshore southern California was subjected to massive contamination by the discharge of as much as 1.9 million kilograms of commercial DDT from the Los Angeles sewer system." This statement is referenced to a publication by MacGregor (*2*) and to a footnote that states that "The estimate of 1.9 million kilograms is based on the measured release of 250 kg/day in 1970" (*3*), and on a subsequent reiteration of this by the Environmental Protection Agency in 1976 (*4*). The report by Carry and Redner does not record a "measured release of 250 kg/day in 1970."

MacGregor bases his estimate on three figures, first, a single aberrant value of 647 pounds (294 kg) in table 6 by Carry and Redner (*3*), which records samples from a sewer receiving influent from Montrose Chemical Company; second, a record of monthly samples taken December 1969 through March 1970, from influent into the Joint Water Pollution Control Plant, which received input from many sources in addition to Montrose; third, the DDT content, estimated at 250 kg/day, of alkaline waste trucked out by Montrose as an alternative procedure (starting in April 1980), replacing the former method of disposal of liquids from a settling pond into the sewers. The alkaline waste had not been allowed to settle (*5*).

Regarding the single aberrant value, the chief engineer of the Los Angeles County Sanitation District stated (*6*) that it represented the "highest ever obtained in the Sanitation Districts' sewerage wastes and cannot be said to represent average conditions of the actual amount of DDT being wasted by Montrose since the Montrose waste stream was not sampled." However, another report (*7*) quotes an analytical value, December 1969, of 5000 parts per billion in the Montrose effluent line with a volume of 280,000 gallons per day, representing DDT discharge of about 5.5 kg/day. Sobelman (*8*) stated that, for 25 years, Montrose's effluents had passed through a settling pond so that the sewer effluent "contained entrained DDT equivalent to about 10–15 lb/day," about 2 percent of the amount reported by Fry and Toone (*1*).

The estimate of 1.9 million kilograms of DDT discharged into the ocean is based on extrapolations that are not well founded.

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