tion in sponges. Electrical coupling has been demonstrated between sponge cells in vitro (*19*), and structures resembling gap junctions have been reported in certain sponges (*20*). Failure to record electrical signals from *Rhabdocalyptus* may be due to purely technical difficulties inherent in the material and need not imply that impulse propagation does not occur (*21*). If impulses must pass by circuitous routes through the porous body of the sponge, conduction velocities measured along strips of body wall would be much lower than those in the primary conducting elements. While it seems most likely that conduction is electrical, as in other excitable tissues, we cannot at present exclude the possibility that conduction in *Rhabdocalyptus* involves some quite novel, nonelectrical signaling mechanism.

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Prenatal Exposure to Synthetic Progestins Increases Potential for Aggression in Humans

Abstract. *Seventeen females and eight males exposed during gestation to synthetic progestins showed a significantly higher potential for physical aggression than their sex-matched unexposed siblings. Exposure to androgen-based compounds appeared to be most closely associated with aggressive responses. There were no differences in verbal aggression or IQ between exposed and unexposed siblings.*

The presence or absence of gonadal hormones early in development affects the expression of a wide variety of sexually dimorphic behaviors in mammals (*1*). For most mammalian species, the organism, regardless of genetic sex, must experience early androgenic stimulation in order to develop many of the behaviors characteristic of males in adulthood, whereas behavior more characteristic of females depends on the relative absence of these gonadal hormones during early development. Reproductive and aggressive behaviors have been clearly documented as hormonally mediated (*1-3*). Evidence is given in this report that human aggression, like aggression in lower mammals, may also be influenced by exposure to steroid hormones early in ontogeny.

In most mammalian species, including humans, males display more intraspecific aggressive behavior under a wider variety of conditions than do females (*4, 5*). Data, particularly from studies of rodents, indicate that exposure to gonadal hormones early in development is linked to a greater likelihood of aggressive display in response to adult testosterone stimulation and to an increased sensitivity to the aggression-promoting property of androgens in adulthood (*2, 3, 6*). Female rhesus monkeys exposed to testosterone during fetal development showed increased frequencies of male-like threat and rough-and-tumble play during the juvenile period (*7*). When these prenatally androgenized females were ovariectomized in adulthood, they displayed significantly more aggressive behavior toward normal females than did animals that had not been exposed to testosterone (*8*). Thus, for many mammals, exposure to gonadal steroids early in ontogeny, whether from an endogenous or exogenous source, appears to be a primary factor in the development of increased aggressive behavior in adulthood.

During the past three decades millions of pregnant women have been treated for threatened abortion with progestins and estrogens (*9*). Evidence that the synthetic progestins administered orally during pregnancy may have some androgenic potential includes reports of (i) masculinization of the genitalia of as many as 18 percent of human female offspring of progestin-treated mothers (*10, 11*) and (ii) virilizing effects on genital morphology of rats treated with both progesterone- and androgen-based synthetic

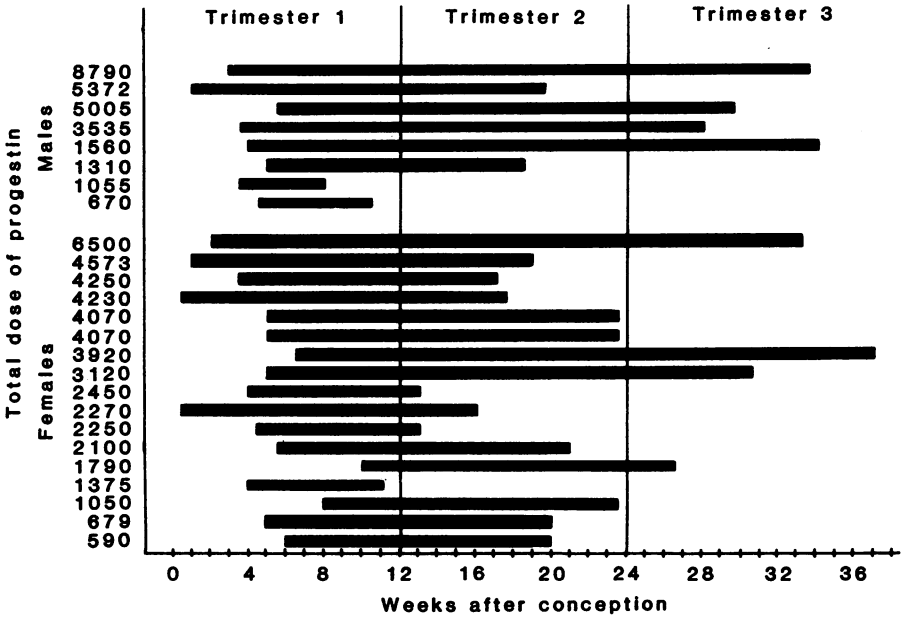

Fig. 1. Duration, timing, and total dose (in milligrams) of exposure to synthetic progestins for male and female human offspring.

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progestins during critical periods of development (*12, 13*).

This study is an evaluation of human subjects that parallels the studies of hormone-mediated aggression in laboratory animals. Seventeen females and eight males, whose mothers were treated with synthetic progestins for complications of this or previous pregnancies, were evaluated on a measure designed to estimate the potential for aggressive behavior. Each of the hormone-exposed subjects was compared to at least one sibling of the same sex who had not been exposed to exogenous hormones. (Siblings provide the best available strategem for matching on genetic and environmental background variables when random assignment to treatment conditions before intervention is precluded.) For four subjects, two siblings of the same sex who had not been exposed to progestins were available, and in these cases the mean score of the siblings was used in comparisons. The mean age of the progestin-exposed females and their unexposed sisters was 11 years, 6 months (range, 6 to 17 years), that of the exposed males and their brothers was 11 years, 4 months (range, 6 to 18 years) (*14*). Because of the expense of this type of prenatal care, the subjects were members of the middle to upper classes (*15*).

The progestins administered to the mothers of hormone-exposed subjects included 19-nor-17α-ethynyltestosterone (19-NET); ethynodiol, an androstenediol-based progestin; hydroxyprogesterone caproate; and medroxyprogesterone acetate. These hormones were administered either singly or in combination. The average total dose of synthetic progestin to which subjects were exposed was 3412 mg (range, 670 to 8790) for males and 2900 mg (range, 590 to 6500) for females. Although the duration and timing of the hormone treatment varied with the physician and the pregnancy history, treatment was initiated in all of the pregnancies during the first trimester, all of the males and 15 of the 17 females being exposed to the hormones before the seventh week of gestation (Fig. 1). Duration of treatment was 4.5 to 31 weeks. Thus, all of the subjects were exposed to the hormones during at least some portion of the period of gestation believed to be critical for hormonal differentiation of genital morphology and the central nervous system in humans (*16*). No virilization of the genitalia was apparent in the progestin-exposed female subjects.

The age-appropriate form of the Leifer-Roberts Response Hierarchy (*17*) and the Wechsler intelligence scales (*18*) were administered individually to each subject. The Response Hierarchy is a paper-and-pencil instrument designed to assess the potential for aggressive behavior by eliciting verbal estimates of the subjects' responses to a variety of common conflict situations. As expected, scores on this measure of aggression potential obtained from subjects aged 4 to 16 years (*17, 19*) and 18 to 20 years (*20*) reveal a sex difference, with males attaining higher physical aggression scores than females. The Response Hierarchy includes six fairly common situations involving interpersonal conflict, originally generated by children and adolescents. Four choices of behavioral response are provided as alternative solutions to each situation: (i) physical aggression, (ii) verbal aggression, (iii) withdrawal, and (iv) nonaggressive coping with the frustrator (including appeal to authority). After each situation is described verbally, the subject is presented with six pairs of forced-choice alternatives in the form of stick figure illustrations representing all possible combinations of the four behavioral responses. In making their choices, subjects are asked to consider each situation as one they have encountered and to choose the response they would have made in that situation. The lowest possible physical aggression score for each situation and the entire measure is 0. If the physical aggression alternative is selected whenever it is presented, a score of 3 for each situation and 18 for the six items is attained.

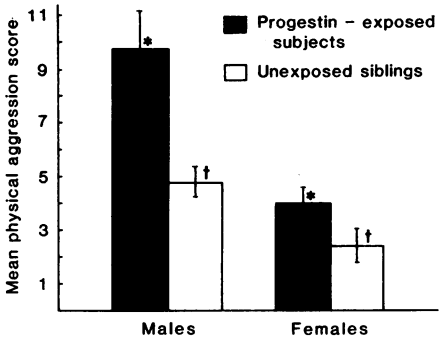

Fig. 2. Mean physical aggression scores for 8 male and 17 female offspring exposed to synthetic progestins and their unexposed sex-matched siblings. Asterisk indicates significant difference between progestin-exposed and unexposed subjects ($P < .01$); dagger indicates significant difference between unexposed males and unexposed females ($P < .02$).

Exposure to synthetic progestins during gestation appears to have a significant effect on subjects' scores on the Response Hierarchy. When progestin-exposed females were compared (paired *t*-tests) to their unexposed sisters, their scores, representing the number of times physical aggression was chosen, were significantly higher ($P < .01$) (Fig. 2). The mean physical aggression score was 4.0 for progestin-exposed females and 2.6 for their unexposed sisters. Of the sibling pairs, 12 progestin-exposed females had higher scores than their sisters, three had scores equal to their sisters, and two scored lower on physical aggression. No difference in the number of verbal aggression responses was found. Males (Fig. 2) exposed prenatally to synthetic progestins also had significantly higher scores than their brothers ($P < .01$). Progestin-exposed males had an average physical aggression score of 9.75, compared to 4.88 for their unexposed siblings. Seven of the progestin-exposed males had higher physical aggression scores than their brothers, and one had a lower score. There was no difference in verbal aggression scores between the progestin-exposed males and their unexposed brothers. The expected significant sex difference was obtained between unexposed males and females ($P < .02$), applying a *t*-test for independent samples.

Neither age nor birth order showed any relation to physical aggression scores. The five males exposed to the androgen-based progestins 19-NET and ethynodiol all had significantly higher scores than their brothers ($P < .02$). Of the four females exposed to 19-NET, three scored higher on physical aggression than their sisters, and the fourth had a score equal to that of her sibling ($P < .068$). The lowest total synthetic progestin dosages were given to the three above-mentioned females exposed to 19-NET, all of whom had higher scores than their sisters. These data are consistent with the observation that 19-NET is the most virilizing of the synthetic progestins on both human (*11*) and laboratory animal (*13*) genital morphology.

As in an earlier report on subjects exposed to progestins prenatally and their sibling controls (*9, 21*), no IQ differences were found between exposed and unexposed siblings. The mean full scale IQ score of this sample was 119.7 for progestin-exposed offspring and 118 for their siblings. As expected, the best predictor of IQ scores for the progestin-exposed subjects was the IQ of their siblings ($r = .48$); thus the subjects were in effect matched for IQ.

The hypothesis that behavior is masculinized by exposure to synthetic progestins during early stages of development is supported by the few studies in which the behavioral effects of these compounds have been evaluated. In studies designed to parallel the investiga-

tion in humans reported here, 19-NET administered prenatally, like testosterone, increased the sensitivity of female mice to the aggression-activating properties of testosterone administered in adulthood and increased the percentage of females that engaged in aggressive behavior (*22*). Zussman *et al.* (*23*) found that boys whose mothers were treated with naturally occurring progesterone during pregnancy were more aggressive in childhood and were more often subjected to disciplinary action in elementary and secondary school than controls. For girls of elementary school age, progesterone administration was associated with a lower incidence of school discipline and tomboyism, but in adolescence the progesterone-exposed girls reported that they got angry more frequently and more intensely than controls (*23*). In another study, 18- to 20-year-old men who had been exposed prenatally to progesterone-based synthetic progestins had elevated hostility scores on the Guilford-Zimmerman Temperament Survey, whereas men exposed to naturally occurring progesterone either alone or in combination with estrogen had lower scores than controls (*24*).

It appears from these and previous data (*5, 17, 19, 20*) that boys and men are more likely than girls and women not only to act aggressively, but also to imagine themselves responding with aggressive behavior to conflict situations. The data presented here suggest that verbal estimates of aggressive response are enhanced in males and females by prenatal exposure to synthetic progestins with androgenic potential. Whether an increased probability of choosing physically aggressive behavior in response to hypothetical conflict situations is related to aggressive action in real life situations has not yet been definitively determined (*17*). Nevertheless, the observation of a relation between augmented prenatal hormone levels and elevated estimates of aggressive response in human females provides additional evidence that many of the principles governing the differentiation of hormone-organized behaviors in laboratory animals may also apply to human behavior. The observed influence of hormones during gestation on later aggressive responses in human subjects suggests that differences in the frequency of aggressive behavior between males and females as well as individual differences may be related to natural variations in hormone levels prior to birth.

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Spontaneous Hypertension in Cross-Suckled Rats

Abstract. *Genetically normotensive Sprague-Dawley rats nursed by spontaneously hypertensive foster mothers develop sustained high blood pressure. Some factor related to the genetically programmed hypertension of the foster mother is probably transmitted to the infant rats through her milk. Alternatively, the hyperkinetic behavior of the mother may activate a hypertensinogen in young having the proper constellation of genes.*

Japanese workers have provided investigators with an intriguing model of genetically programmed hypertension: the spontaneously hypertensive (SH) rat (*1–3*). These rats are of interest to experimentalists and clinicians because they provide close facsimiles of essential hypertension in the human. Although there is no doubt that the spontaneous hypertension in these rats is due to peripheral vasoconstriction and myocardial hemodynamic changes, some investigators believe that nutritional and hormonal alterations may play a conditioning role in the genetic expression of the hypertension (*4*). We and others (*4*) have found that a diet high in calories and fat or a greatly reduced food intake inhibits spontaneous hypertension in SH rats and that hypophysectomy, adrenalectomy, and gonadectomy inhibit the development of high blood pressure if performed shortly after weaning.

The SH rat is born normotensive, but at 4 to 5 weeks of age its blood pressure begins to rise, reaching abnormally high levels by 120 days of age. We attempted to correlate changes in nutritional and hormonal vectors with the pathogenesis of hypertension from the time of weaning and the early steep ascent of blood pressure. The Wistar-Kyoto (WKy) rat is generally purported to be the normotensive counterpart of the SH rat. However, when we transplanted pituitary and adrenal glands from young SH rats into

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