POST-PUBERTAL EFFECTS OF PRENATAL ADMINISTRATION OF PROGESTERONE

John Unger Zussman Patti Peters Zussman

Stanford University

and

Katharina Dalton

University College Hospital

Abstract

Recent interest has focused upon the role of hormones, particularly early hormones, in behavior and development. A distinction which has sometimes been unclear is one between the hormone progesterone and progestins, the group of gestation-inducing steroids of which progesterone is the naturally occurring hormone. Prenatal administration of synthetic progestins, unlike progesterone, has been found to have masculinizing effects on the female fetus (Money and Ehrhardt, 1972). The present investigation explored the effects of prenatal progesterone on post-pubertal subjects in a variety of psychological and maturational areas.

A sample was identified of 16-19-year-old British and Irish children whose mothers, when pregnant, had been administered varying doses of progesterone to prevent toxemia of pregnancy (N=30; 18 males, 12 females). A control sample (N=29; 17 males, 12 females) was also selected and contacted. The subjects were interviewed and given a set of psychological and cognitive in-

ventories.

Results showed that high dosage and early administration of progesterone related to somewhat delayed onset of puberty in boys and girls. Progesterone administration was also significantly associated in both sexes to higher levels of performance on mathematical and spatial problems, extending Dalton's (1968) findings of higher school achievement for progesterone children at ages 9-10 years. Along with this greater intellectual inclination, the progesterone Gs seemed less oriented to intensive social activity. They reported less extensive heterosexual activity than did control Gs, as well as having less influence on other people. Dosage and early administration of progesterone also related significantly to self-reported incidence of tomboyism in females, with Gs who received larger and earlier doses of progesterone reporting less tomboyism between ages 5-10 years. No cases of obviously abnormal physical or psychological sexual adjustment appeared in the sample.

Several explanations for the data are proposed, suggesting interesting avenues for further research.

PLEASE DO NOT PUBLISH WITHOUT PERMISSION

POST-PUBERTAL EFFECTS OF PRENATAL ADMINISTRATION OF PROGESTERONE*

John Unger Zussman Patti Peters Zussman

Stanford University

and

Katharina Dalton

University College Hospital, London

Introduction

Recent interest has focused upon the role of hormones, particularly early hormones, in behavior and development. A distinction which has sometimes been unclear is one between the hormone progesterone and progestins (progestogens), the group of gestation-inducing steroids of which progesterone is the naturally occurring hormone. Three major functions of progesterone have been identified: (1) to induce and support gestation; (2) to prepare the endometrium during the second half of the menstrual cycle for implantation of the fertilized egg; and (3) to serve as a building block for other steroids, including testosterone and estrogen. Unlike progesterone, synthetic progestins cannot fulfill this third, "building block" function (Dalton, 1971).

---

* Paper presented at the meeting of the Society for Research in Child Development, Denver, April 1975. The study was conducted while the first author held a National Science Foundation Graduate Fellowship, and was partially supported by the Haas Fund at Stanford University. We are grateful to Keith Brodie, Norman Fisk, Eleanor Maccoby, and to our subjects and their parents for their aid and support. First two authors' address: Department of Psychology, Stanford University, Stanford, California 94305.

Prenatal administration of synthetic progestins has been found to have physically and psychologically masculinizing effects on the female fetus, in the syndrome called "progestin-induced hermaphroditism" (Money and Ehrhardt, 1972). However, no ill effects on the fetus have been reported for progesterone (Jost, 1973). Indeed, Dalton (1968) has reported developmental advancement at one year, and greater academic achievement at 9-10 years, among children who received prenatal progesterone. The present investigation was conducted to explore the effects of prenatal progesterone on post-pubertal subjects in a variety of intellectual, psychological, and maturational areas.

Method

Mothers of the progesterone children in this study had been administered at least 500 mg of progesterone during pregnancy for the relief of symptoms of pre-eclamptic toxemia, in which it has been found to be effective (Dalton, 1957, 1962). Progesterone children and controls were drawn from two sources: (1) Hospital. At City of London Maternity Hospital, progesterone was regularly administered for toxemic symptoms during the period when these children were born. Each progesterone child was included in the study population, along with the next-born child in the labour ward register whose mother had a normal pregnancy (normal control), and the next child born of a mother who developed toxemia (toxemic control). These were the children whose academic achievements at age 9-10 were reported by Dalton (1968). (2) General practice. All progesterone children from a general medical practice in North London were matched for sex, birthweight, SES, blood group, mother's age, and family size with a normal

control from the practice. No toxemic controls were available from this source.

The total identified population included 65 progesterone children and 96 controls, 16-19 years old when the testing was conducted. All of the families lived in North London through at least the first nine years of the child's life (at testing some families had moved into other parts of Southern England or to Ireland), and were generally working-class. All children were sent letters asking for their participation in the study. The final sample of subjects interviewed included 30 progesterone children (12 females, 18 males) and 29 controls (12 females, 17 males).

Two interviewers, blind to Ss' treatment conditions, arranged and conducted the testing, usually at the subject's home. The testing of each child lasted about 1-1/2 - 2 hours and included the following areas:

(1) Brief biographical and demographic information.

(2) 10-12 problems from each of the following Differential Aptitude Test subscales:

   (a) Verbal Reasoning.

   (b) Numerical Ability.

   (c) Abstract Reasoning.

   (d) Mechanical Reasoning.

   (e) Spatial Reasoning.

(3) 6 figures from the Embedded Figures Test.

(4) The masculinity-femininity scale from the California Psychological Inventory, somewhat modified for British subjects.

(5) The Bem Sex-Role Inventory (Bem, 1974).

(6) A short questionnaire on physical development.

(7) A structured interview, lasting approximated 1/2 hour, tapping S's activities, interests, social life, and perceived personality characteristics. About a third of this interview concerned S as he/she was at age 5-10; the remainder focused on his/her current characteristics.

Results

Effects of prenatal progesterone were assessed by analyses of (1) mean differences between progesterone and control groups, and (2) relationships between dependent variables and progesterone dosage (range 0.5 gm - 9.4 gm among progesterone Ss), duration of administration (range 1 week - 34 weeks of treatment), and timing of first administration (range 6th week of pregnancy - 39th week).

Cognitive development

In the cognitive areas, there were some complications in direct comparisons between progesterone and control group means due to a differential dropout rate. On the basis of previous information on the subjects, it was clear that the non-inclusion rate was not random, and that it was the less intellectually able individuals who were more likely to drop out of the control group. We are currently attempting to take account of this problem in our analyses, but for today's presentation we will concentrate on the relationships between cognitive measures and progesterone dosage, duration, and timing of administration.

On the Differential Aptitude Test, a clear advantage in Numerical Ability was found to be associated with progesterone administration. Table 1 illustrates the relationship between numerical score (dichotomized at

the median) and dosage (dichotomized at the median for progesterone Ss, with high dosage defined as 3.0 gm or more). The advantage with higher

---

Table 1 about here

---

progesterone dosage was highly significant ($\chi^2 = 11.53$, df = 2, p = .003). A similar advantage was found for Ss who received progesterone over a period longer than 8 weeks ($\chi^2 = 7.53$, df = 2, p = .023). This relationship between progesterone administration and numerical ability was particularly striking for females. There were several marginally significant relationships showing borderline positive effects of progesterone on spatial and mechanical ability. There were no such trends for verbal ability, however, and in fact one reversal for abstract reasoning in boys.

Personality and social development

We had set out to explore any masculinizing or feminizing influences that prenatal progesterone might have had on our adolescent subjects. Unfortunately, it was impossible to perform any sort of genital examinations of the subjects. However, no cases of obviously abnormal physical development or psychosexual adjustment appeared in the sample. Prenatal progesterone administration did not relate significantly to masculinity-femininity scores on the Bem Sex-Role Inventory or the California Psychological Inventory for either sex.

In general, few significant differences were found between progesterone and control Ss in analysis of data from the structured interview, confirming the normality of the progesterone Ss. However, the differences that did appear seemed to form an interesting pattern.

The most striking finding from the interview was in responses of females to the question: "Would you have considered yourself a tomboy at age 5-10?" Table 2 reports the biserial relationships between these responses and the progesterone variables. Female Ss who received larger,

---

Table 2 about here

---

longer, and earlier doses of progesterone were less likely to report having been a tomboy at this age.

On other variables dealing with S at age 5-10, progesterone females also reported having been more concerned with their appearance than controls ($p < .05$), and early administration was associated with females having preferred long hair to short ($p < .05$). Dosage, duration, and early administration related negatively to reports of discipline in school at this age for females ($p < .05$), but positively for males ($p < .05$). Higher dosage and longer administration of progesterone were negatively associated with influence over peers at this age ($p < .05$), particularly for females; while children with higher dosage reported playing in larger groups ($p < .05$), particularly males. Activity of interests and play (athletic, outdoor, motile types of play) at age 5-10 was negatively associated with dosage, duration ($p < .05$), and early administration ($p < .10$) for both sexes.

Reliable differences found in current characteristics were related to heterosexual activity. Progesterone Ss, especially males, reported less daydreaming about the opposite sex ($p < .05$). Progesterone males also reported dating less often ($p < .05$), and thinking less about marriage and family life ($p < .01$), than control males. Among males, early administration

of progesterone was associated with decreased frequency of going steady ($p < .01$), as well as an increased likelihood of reporting school discipline ($p < .05$).

Discussion

It was found that prenatal progesterone administration significantly enhanced performance on mathematical problems, with borderline positive effects in other areas of intellectual competence. Dalton (in preparation), analyzing the performance of these and other subjects on the English public school leaving examinations, found a higher level of achievement among progesterone children relative to controls, particularly in the mathematics and sciences. Remarkably, 32% of progesterone Ss obtained a university place, compared to figures of 6.1% among control Ss and 6.3% for London in general. These results confirm and extend Dalton's (1968) findings of higher school achievement for an overlapping sample at age 9-10. This greater intellectual inclination for the progesterone children is particularly noteworthy in view of the fact that toxemia of pregnancy is normally associated with diminished intelligence in the child (Dalton, in preparation).

The findings for personality and social development suggest that these children may be somewhat less oriented toward intense social activity than control Ss. This orientation appears in our progesterone Ss' reports that at age 5-10 they engaged in less active play, and had less influence over peers, than control Ss. Progesterone in females also related to receiving less discipline in school, and decreased likelihood of having been a tomboy at this age. This latter finding directly contrasts with Money and Ehrhardt's

(1972) results on tomboyism among progestin-induced hermaphroditic females, confirming the distinction between progesterone and synthetic progestins. Decreased social orientation is also suggested by our findings of less current heterosexual activity among progesterone Ss, notably among males. Progesterone males also seemed to have a somewhat less easy social adjustment in school, reporting more discipline at both ages.

We may ask if there is any evidence here that prenatal progesterone has masculinizing or feminizing effects on either sex. In intellectual ability, progesterone seems to have positive effects in areas in which males normally excel---mathematical, mechanical, and spatial ability. On the personality and social variables, as discussed earlier, our progesterone Ss played less actively with peers at age 5-10, were less likely to be tomboys at this age if female, and displayed less current heterosexual interest, especially if male. These differences might be interpreted as suggesting a masculinizing effect in cognitive areas and a feminizing effect, in a certain sense, in personality-social development. However, there was no evidence of effeminacy in any other sense, and no effects of progesterone were found on two masculinity-femininity scales. We are inclined to believe that the hypothesis that progesterone Ss are more studious and less socially interactive than controls, is a more parsimonious and complete explanation for these data than a hypothesis of selective masculinization and feminization in different areas.

The causal processes underlying these results remain unclear for the present. It is possible that progesterone acts on the fetal brain to facilitate cognitive development, and that making use of this increased cognitive capacity may draw the progesterone child away from social pur-

suits. Or the reverse process may be operative, with progesterone predisposing the child toward less intense social interaction, from which he/she may turn toward intellectual activity. A third possible explanation, which we are currently investigating, is that prenatal progesterone may somewhat delay the onset of puberty, which in turn may decrease social activity and increase intellectuality. What is clear is that the evidence strongly supports the long-term influence of progesterone on the fetal brain, particularly with higher dosage, longer duration of administration, and early administration. Dalton (in preparation) has suggested that administration of progesterone may operate by causing an "overnutrition" and increased production of cells in certain parts of the brain controlling learning ability. An additional possibility, relying on the unique "building block" function of progesterone, is that the administered progesterone is processed into other corticosteroids which may also affect the brain.

Further research should attempt to replicate these findings, particularly since the studies showing heightened cognitive achievement in progesterone children have used overlapping samples. Extensive research is also needed to sort out the causal processes operating in these data.

References

Bem, S.L. The measurement of psychological androgyny. Journal of Consulting and Clinical Psychology, 1974, 42, 155-162.

Dalton, K. Toxaemia of pregnancy treated with progesterone during the symptomatic stage. British Medical Journal, 1957, 2, 378-381.

Dalton, K. Controlled trials in the prophylactic value of progesterone in the treatment of pre-eclamptic toxaemia. Journal of Obstetrics and Gynaecology of the British Commonwealth, 1962, 69, 463-468.

Dalton, K. Ante-natal progesterone and intelligence. British Journal of Psychiatry, 1968, 114, 1377-1382.

Dalton, K. Puerperal and premenstrual depression. Proceedings of the Royal Society of Medicine, 1971, 64, 1249-1252.

Dalton, K. Pre-natal progesterone and educational achievement. Manuscript in preparation.

Jost, A. Hormonal effects on fetal development: A survey. Clinical Pharmacology and Therapeutics, 1973, 14, 714-720.

Money, J. and Ehrhardt, A.A. Man and Woman, Boy and Girl. Baltimore: Johns Hopkins University Press, 1972.

John Unger Zussman, Patti Peters Zussman, and Katharina Dalton

Post-pubertal effects of prenatal administration of progesterone

Table 1

Number of subjects scoring high and low on numerical D.A.T. problems, by progesterone dosage

Progesterone dosage	Numerical score: High	Numerical score: Low
High (≥ 3.0 gm)	14	1
Low (< 3.0 gm)	7	8
Control	12	17

($\chi^2 = 11.53$, df = 2, p = .003)

Table 2

Biserial relationships between self-reported tomboyism at age 5-10 (female subjects) and progesterone variables

Variable	Kendall τ
Dosage (gm)	-.39**
Duration of administration (weeks)	-.40**
Earliness of administration (weeks before birth)	-.36*

(N = 24; * $p < .05$; ** $p < .01$)

Figure 1

Effects of Progesterone Dosage and Duration on Cognitive Test Scores

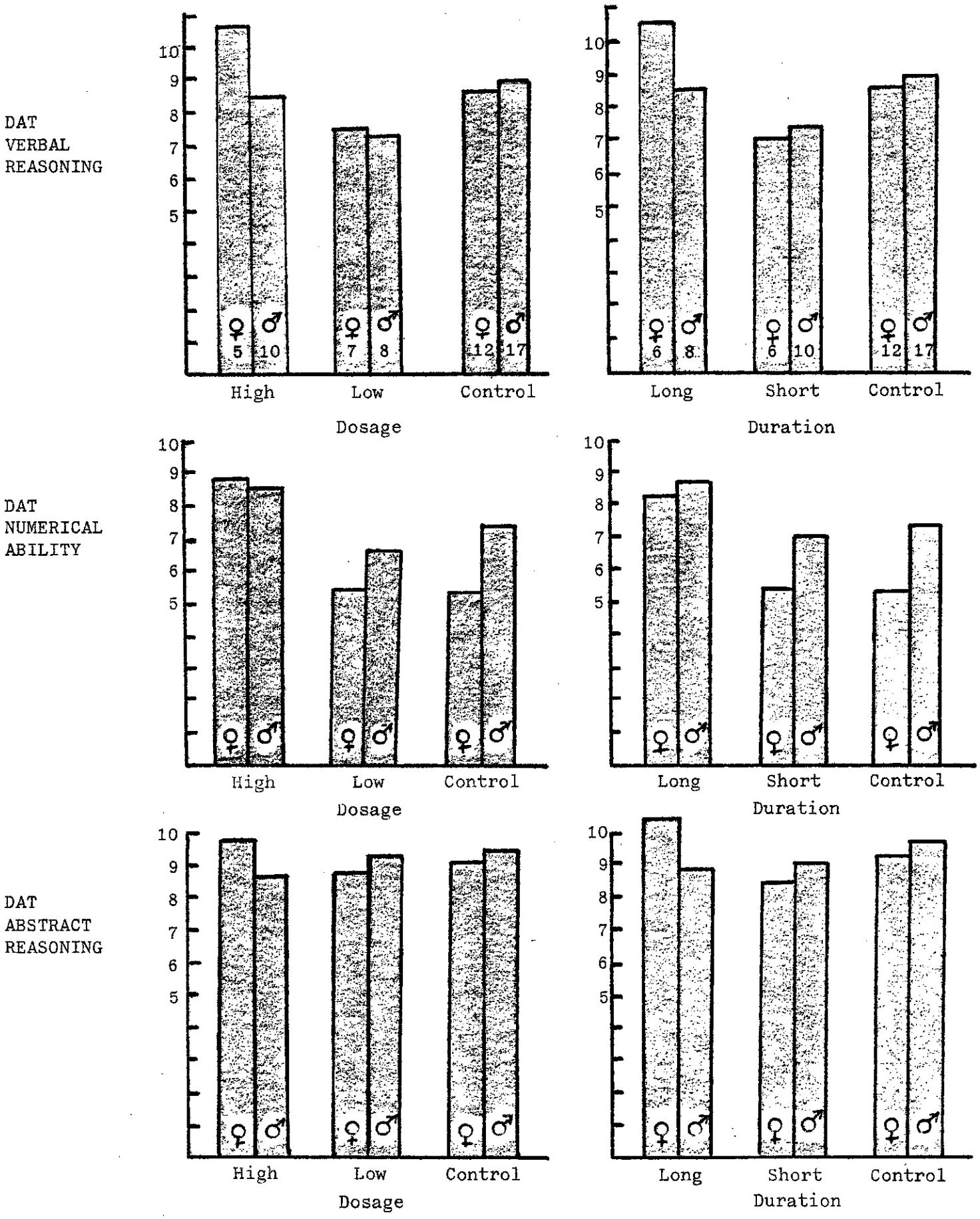
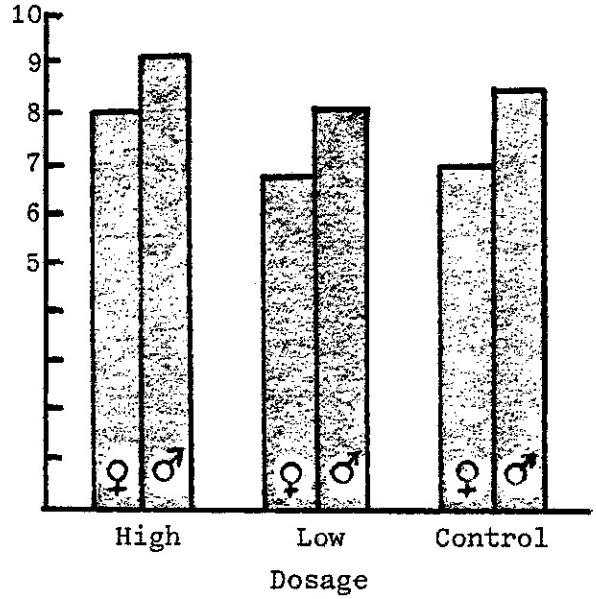
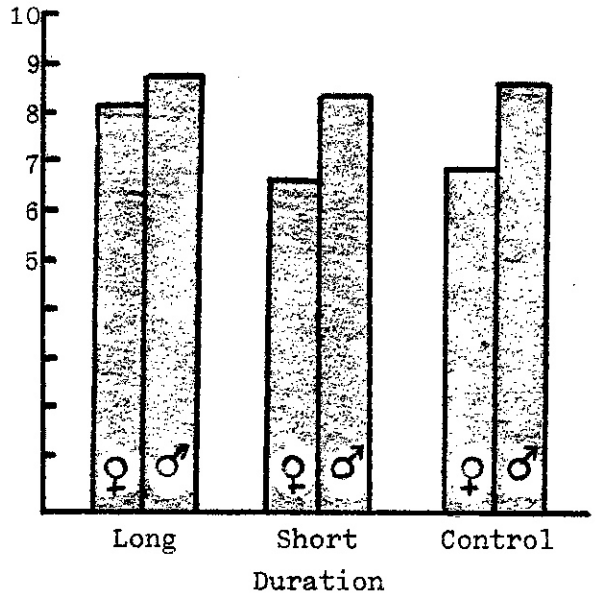


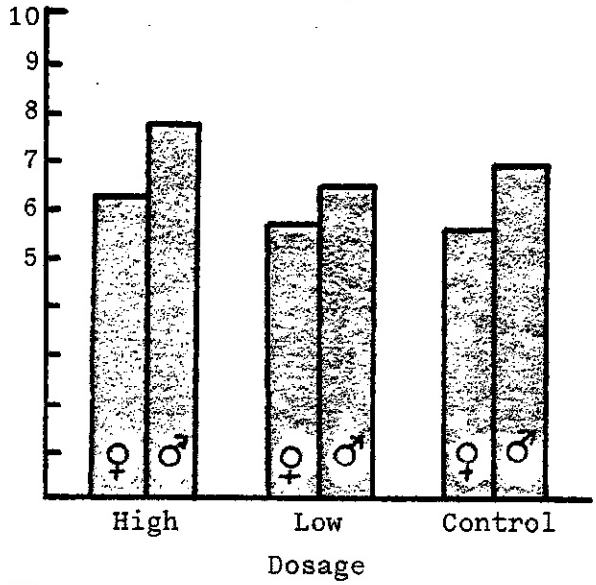
Figure 1 (continued)

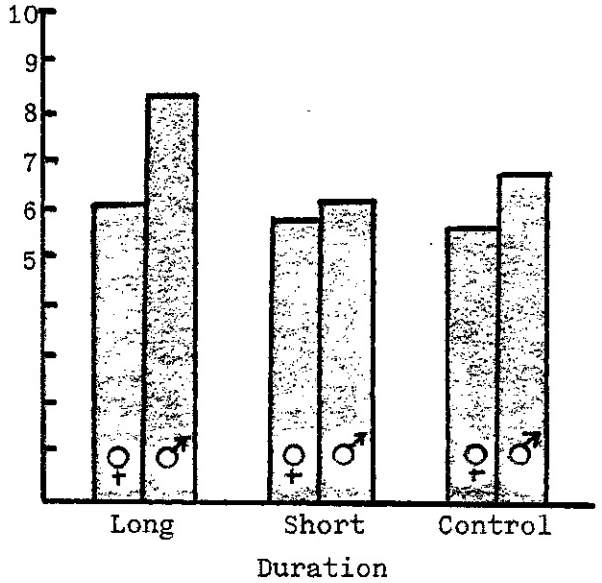
DAT MECHANICAL REASONING





DAT SPATIAL REASONING





EMBEDDED FIGURES TEST (seconds)