lies differ in the percentage of mothers with some formal education (Table 1). More important, since school attendance was compulsory until the eighth grade, older children in the large families may soon have surpassed their parents in their ability to educate and help the younger children in the family. This hypothesis is verified by data from questionnaires obtained from a representative sample of 4321 Israeli sixth-grade children in 1973. With the number of older children held constant and with decreasing formal education for the parents, children are more likely to report that an older sibling rather than a parent helps with homework and takes an interest in school activities. For example, when the child has two older siblings and neither parent has formal schooling, about 88 percent report that an older sibling rather than a parent helps with homework. The corresponding figure when at least one parent studied beyond high school is 31 percent.

A process by which children overtake their parents in providing intellectual stimulation for younger siblings could be described by the confluence model, either in its original or revised version (*7*). However, accurate simulation by the model of our data would require that the rate parameters be greatest in large Oriental families. An alternative approach would view intellectual development as a function of the external as well as the home environment. This approach does not contradict the model but adds a component of intellectual development that is independent of the intellectual environment of the home. This component should be particularly evident in rapidly developing cultural groups or societies in which educational institutions provide greater intellectual stimulation than parents do.

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15 December 1976; revised 4 March 1977

Cannabinoids Inhibit Testosterone Secretion by Mouse Testes in vitro

Abstract. *Addition of delta-9-tetrahydrocannabinol or cannabinol to an incubation medium containing decapsulated mouse testes caused a significant reduction in the accumulation of testosterone in the medium. This result suggests that the reported effects of cannabis on male sexual and reproductive function may result from direct inhibition of testicular steroidogenesis by both psychoactive and nonpsychoactive constituents of marihuana.*

Marihuana and its psychoactive constituent, delta-9-tetrahydrocannabinol (THC), have been implicated in the alteration of testicular function in several species including man. Administered through various routes, either marihuana or THC can reduce the concentration of testosterone (T) in peripheral plasma in both rat and man (*1, 2*), suppress spermatogenesis and produce changes in sperm-head proteins (*3, 4*), and reduce the weight of the testes and the accessory reproductive organs (*3–5*). A reduction in certain androgen-dependent behavioral responses, such as intra- and interspecies aggression (*6*) and copulatory behavior in male rats and mice (*7*), has also been observed. In men, reduced sexual potency and gynecomastia (*1, 2, 8*) have been reported in heavy marihuana users. However, changes in aggressive and sexual behavior induced by cannabinoids may be related to the action of these compounds on higher brain centers rather than to changes in the function of the hypothalamic-pituitary-testicular system.

Cannabis-related decreases in peripheral luteinizing hormone (LH) and prolactin levels (*1, 2, 9*) suggest that alteration in testicular function may be secondary to suppression of the pituitary. Increased adrenal weight (*5*) and corticosterone production (*10*) with cannabis treatment suggest another possible mechanism for the alteration in testicular function.

In contrast, the demonstration of an inhibitory effect of THC, cannabinol (CBN), and other cannabinoids on the synthesis of protein and nucleic acid in incubated testicular slices (*11*) suggests that THC may act directly on the testis. We therefore studied whether these cannabinoids are capable of directly affecting the testicular biosynthesis of T in vitro. We examined the effects of THC and CBN (which is believed not to be psychoactive) using decapsulated mouse testes in an in vitro incubation system.

Adult (2 to 3 months of age) or immature (34 to 37 days) closed-colony but not inbred laboratory mice were killed by cervical dislocation; the testes were immediately removed, decapsulated, and incubated in Krebs-Ringer bicarbonate buffer, glucose (1 mg/ml), and 12.5×10^{-3} international unit of human chorionic gonadotropin (Follutein, Squibb) per milliliter (*12*). The THC or CBN, at the various doses, was introduced into the incubation medium in a 20-μl volume of ethanol. The same amount of ethanol was added to the control flasks. The concentration of T in the medium after 4 hours of incubation was determined by radioimmunoassay (*13*) after suitable dilution of the aliquot (*14*). As a control, mouse testes were incubated either with ethanol (at doses of 10, 20, or 50 μl/ml) or without ethanol. At these doses, ethanol did not affect T release. The differences between the mean T concentration in alcohol-containing and in control incubations were no greater than 9 percent and were not significant.

The effect of THC on testes obtained from adult mice is shown in Table 1. The

Table 1. Effects of treatment with Δ^9-tetrahydrocannabinol (THC) in vitro on the production of testosterone (T) by the decapsulated testes of adult (2- to 3-month-old) and immature (34- to 37-day-old) mice. The results represent mean (± S.E.) concentration of T in the incubation medium at the end of a 4-hour incubation. The size of each treatment group is shown in parentheses. Abbreviation: N.S., not significant.

Concentration of THC (μg/ml)	Age of mice	Concentration of T (ng/ml)		Inhibition (%)	P
		Controls	Treated		
0.25	Adult	517 ± 58 (8)*	386 ± 27 (8)	25	< .05
2.5	Adult	517 ± 58 (8)*	426 ± 37 (8)	18	N.S.
12.5	Adult	225 ± 24 (11)	159 ± 10 (11)	29	< .02
25	Adult	517 ± 58 (8)*	71 ± 16 (8)	86	< .001
25	Immature	253 ± 33 (12)	118 ± 16 (12)	53	< .001

*Listing identical control values more than once represents comparison of several treatment groups to one control group, all run in a single incubation.

addition of THC in a 20-μl volume of ethanol, to the incubation medium, in order to achieve THC concentrations of 0.25, 2.5, 12.5, or 25 μg/ml resulted in 25, 18, 29, or 86 percent inhibition, respectively, in the accumulation of T in the incubation medium. In another experiment, with testes obtained from immature mice, the dose of 25 μg THC per milliliter resulted in a 53 percent decrease ($P < .001$) in the accumulation of T (Table 1). In a subsequent experiment with adult animals, the addition of 25 or 250 μg CBN per milliliter of incubation medium significantly ($P < .001$) inhibited the production of T (Table 2). These results complement the findings of Jacubovic and McGeer (*11*), who demonstrated that THC, CBN, and other cannabinoids can inhibit the synthesis of nucleic acids, proteins, and lipids in testicular slices in vitro.

Recently, THC has been shown to possess estrogenic activity (*15*), and some investigators have suggested that estrogens may inhibit testosterone synthesis by a direct action on the testis (*16*). However, in this incubation system, the addition of estradiol, at doses as high as 5 μg/ml, did not affect T accumulation in the incubation medium (*17*).

It is always difficult to extrapolate from experiments conducted in vitro to conditions in vivo. Although THC can concentrate in testicular tissue (*18*), the actual in vivo concentrations in human marihuana users, or in experimental animals treated with cannabinoids, may vary considerably from those used in this study. However, the results do indicate that (i) THC, in a wide range of doses (including the relatively low level of 0.25 μg/ml), can significantly reduce T biosynthesis in the decapsulated mouse testis and (ii) CBN can have a similar effect.

The ability of either cannabis or THC to lower plasma T levels in vivo has been described (*1, 2*). We have observed that subcutaneously injecting male mice with 100 μg CBN per day for 4 days significantly reduced T levels in the plasma sampled approximately 5 hours after the last injection (1.73 ± 0.75 versus 8.50 ± 2.26 ng/ml; $P < .02$) (*19*). The similarity of the response of mouse testes in vitro to both THC and CBN suggests that nonpsychoactive constituents of cannabis can contribute to its effects on the endocrine system. Furthermore, suppression of testicular function by CBN, or other nonpsychoactive components of marihuana, could account for some of its effects on androgen-dependent behaviors.

The mechanism of action of marihuana on testicular function remains to be elucidated, but our results indicate that the reduction in peripheral T levels observed in vivo (*1, 2*) impaired spermatogenesis (*3, 4*), and decreases in androgen-dependent behaviors (*6, 7*) may be due, at least in part, to a direct inhibitory effect of cannabinoids on the production of T by the testis.

Table 2. The effect of treatment with cannabinol (CBN) in vitro on the production of testosterone (T) by the decapsulated testes from adult mice. The results represent mean (± S.E.) concentration of T in the incubation medium at the end of a 4-hour incubation.

CBN concentration (μg/ml)	T			
	ng/ml	*N*	Inhibition (%)	*P*
	368 ± 27	9		
25	99 ± 10	9	73	< .001
250	18 ± 5	8	95	< .001

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30 November 1976; revised 17 January 1977

Suppression of Sympathetic Nervous System During Fasting

Abstract. *Two days of fasting in rats significantly reduces the turnover of norepinephrine in the heart. In contrast to the effects of ganglionic blockade in fed controls, similar blockade in fasted animals is without significant effect on [^{3}H]-norepinephrine retention or endogenous norepinephrine in the heart. These data are consistent with suppression of centrally mediated sympathetic activity in the fasted state. The decrease in norepinephrine turnover during fasting is completely reversed by 1 day of refeeding.*

Measurement of norepinephrine (NE) turnover provides a direct, in vivo means of quantifying the activity of the sympathetic nervous system in different sympathetically innervated organs. The sympathetic neurotransmitter, NE, is synthesized and stored within the peripheral sympathetic nerve endings. In response to nerve impulses NE is released from the nerve ending to stimulate the effector cells within its microenvironment. The action of released NE is terminated by an active transport mechanism within the membrane of the sympathetic nerve terminal. This uptake process conserves transmitter and, together with de novo biosynthesis of NE, serves to maintain the level of NE within a narrow range. The endogenous level of NE within a particular tissue does not, therefore,