dopamine, formed by the decarboxylation of 3-*O*-methyl-dopa, may play a role in the actions of L-dopa. For example, *O*-methylated metabolites including 3-*O*-methyl-dopamine, enhance the uptake of norepinephrine into adrenergic nerve endings (*12*).

Methods of potentiating the effect of a dose of L-dopa have been under consideration for some time. Thus, inhibitors of the peripheral decarboxylation of L-dopa enhance the conversion of the precursor to catecholamines in the brain (*13*). Methyl-group acceptors or inhibitors of methyl transfer might similarly be of use in potentiating the clinical efficacy of L-dopa.

R. J. WURTMAN
C. M. ROSE
Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge 02139
S. MATTHYSSE, J. STEPHENSON
R. BALDESSARINI
Laboratory of Neuropsychopharmacology, Massachusetts General Hospital, Boston

References and Notes

1. A. Carlsson, M. Lindqvist, T. Magnusson, B. Waldeck, *Science* **127**, 471 (1958); G. F. Murphy and T. L. Sourkes, *Arch. Biochem. Biophys.* **93**, 338 (1961); R. J. Wurtman, *Catecholamines* (Little, Brown, Boston, 1966).
2. H. Ehringer and O. Hornykiewicz, *Klin. Wochenschr.* **38**, 1236 (1960); O. Hornykiewicz, *Pharmacol. Rev.* **18**, 925 (1966).
3. W. Wiener, W. Harrison, H. Klawans, *Life Sci.* **8**, 971 (1969).
4. D. B. Calne, F. Karoum, C. R. J. Ruthven, M. Sandler, *Brit. J. Pharmacol.* **37**, 57 (1969).
5. C. M. Rose, C. Chou, R. J. Wurtman, *Fed. Proc.* **29**, 511 (1970).
6. J. Axelrod and R. Tomchick, *J. Biol. Chem.* **233**, 702 (1958).
7. R. J. Baldessarini and I. J. Kopin, *J. Neurochem.* **13**, 769 (1966).
8. D. Reis and R. J. Wurtman, *Life Sci.* **7**, 91 (1968); R. W. Piepho and A. H. Friedman, *Pharmacologist* **11**, 255 (1969); M. J. Zigmond and R. J. Wurtman, *J. Pharmacol. Exp. Ther.* **172**, 416 (1970).
9. J. Glowinski, I. J. Kopin, J. Axelrod, *J. Neurochem.* **12**, 25 (1965); J. Glowinski and R. Baldessarini, *Pharmacol. Rev.* **18**, 1201 (1966).
10. G. C. Cotzias, P. S. Papavasiliou, R. Gellene, *N. Engl. J. Med.* **280**, 337 (1969).
11. W. C. Rose, M. J. Coon, H. B. Lockhart, G. F. Lambert, *J. Biol. Chem.* **215**, 101 (1955).
12. L. Iversen, J. Fisher, J. Axelrod, *J. Pharmacol. Exp. Ther.* **154**, 56 (1966).
13. G. Bartholini and A. Pletscher, *ibid.* **161**, 14 (1968).
14. Supported in part by grants from NASA (NGR-22-009-272), NIH (MH-16674-02), and the Scottish Rite Program of Research in Schizophrenia. We thank C. Chou for technical assistance.

11 May 1970

Height and Weight at Menarche and a Hypothesis of Critical Body Weights and Adolescent Events

Abstract. *Height and weight at menarche were found for each subject in three longitudinal growth studies. Early and late maturing girls have menarche at the same mean weight, but late maturers are taller at menarche. Two other major events of adolescence, initiation of the weight growth spurt and maximum rate of weight gain, also occur at an invariant mean weight. The hypothesis is proposed that a critical body weight may trigger each of these adolescent events. Such an interaction would explain the secular trend to an earlier menarche.*

We analyzed the adolescent growth spurt by determining the height and weight for each child at the age of initiation of the spurt in growth (*1*), and at the time of maximum rate of growth (*2*), using the data from three longitudinal (each child is measured at each successive age) growth studies (see *3*).

The mean weight of girls at the time of initiation of the spurt in weight growth, about 31 kg (68 lb), did not differ for early and late maturing girls (*4*), whereas the mean height at the time of the initiation of the spurt in height growth increased significantly (about 10 cm) with age of initiation (*1*). [The height and weight spurts begin practically simultaneously (*1*).] Similarly, at the time of maximum rate of weight gain, the mean weight of early and late maturing girls was the same, about 39 kg (86 lb), whereas the mean height increased significantly with age of maximum rate of height gain (*2*).

These results account for the many observations (*5*) that early maturers have more weight for height than late maturers before and throughout the adolescent growth spurt. What was unexpected, however, was that two of the major events of adolescence were related to an unchanging mean weight. We have now found that a third adolescent event, menarche, also occurs at an unchanging mean weight.

Menarche occurs after the adolescent maximum rates of growth in height and weight are attained (*2*). As far as we know there are no data on actual height or weight at menarche, although there are many general observations that girls at menarche are taller and heavier than those of the same age who have not achieved menarche (*5*).

We estimated weight and height at menarche for 181 girls of the three growth studies by interpolation of their height and growth data (*6*). The mean age of menarche of all girls is 12.9 ± .09 years; their mean weight at menarche is 47.8 ± .51 kg (106 lb); their mean height at menarche is 158.5 ± .50 cm. The mean height increases significantly ($P < .02$) from 156.4 ± .97 cm to 160.9 ± 1.4 cm as the mean age of menarche increases from 11.4 to 14.5 years. [If HSPH girls, who we know from (*2*) include unusually short latest maturers, are excluded, the means are 156.7 ± 1.2 cm and 162.1 ± 1.6 cm ($P < .01$).] The mean weight at menarche, 48 kg, does not change with increasing age of menarche (Table 1).

Early maturers grow more rapidly in height and weight than late maturers during the adolescent spurt (*7, 8*). We find they continue to do so during the year of menarche: the increments in height and weight in that year are 7.0 ± .24 cm and 6.8 ± .46 kg, respectively, for girls with a mean age of menarche of 11.4 years; they decrease gradually to 3.8 ± .21 cm and 4.2 ± .35 kg for girls with a mean age of menarche of 14.5 years (difference significant at $P < .01$).

We observed, as did Shuttleworth (*7*), that late maturers take longer to attain menarche after initiation of the growth spurt; as the mean age of menarche increased from 11.4 to 14.4 years, the time increased from 2.9 ± .19 to 3.6 ± .18 years (*1*). Late maturers also take longer to attain menarche after attainment of maximum rate of growth (*2, 7, 8*). It has been suggested that these time differences are possibly not real, but are statistical artifacts (*9*). Our data show that the observed longer intervals must be real; since late maturers attain all the critical events at the same weight as early maturers and grow more slowly, they necessarily take a longer time between events and from initiation to menarche.

At age 18, when growth in height has ceased for all girls (*2*), early and late maturers are the same height (Table 1) (*1, 2, 10*), but late maturers are lighter in weight (Table 1) (*1, 2, 7*), and remain so into adulthood (*2*; *5*, p. 97). These results at age 18 are expected from the findings previous to and at menarche: early and late maturers can achieve the same height at age 18 since the early maturers, though shorter,

Table 1. Mean age of menarche and mean height and mean weight at menarche and at age 18 for girls of CRC, BGS and HSPH growth studies grouped by age of menarche.

Age (yr)	No.	At menarche: Mean age (yr)	At menarche: Mean height (cm)	At menarche: Mean weight (kg)	At 18 years old: Mean height (cm)	At 18 years old: Mean weight (kg)
Up to and incl. 11.9	35	11.4	156.4 ± .97	47.9 ± 1.1	165.9 ± 1.1	59.5 ± 1.5
12.0–12.9	60	12.4	158.0 ± .73	48.7 ± .95	165.8 ± .71	58.4 ± .99
13.0–13.9	54	13.4	159.1* ± 1.0	47.2 ± .93	165.2 ± .95	55.9 ± .89
14.0–14.9	32	14.5	160.9† ± 1.4	47.2 ± 1.2	165.8 ± 1.4	54.3‡ ± 1.4
All subjects	181	12.9 ± .09	158.5 ± .50	47.8 ± .51	165.6 ± .48	57.1 ± .57

* Difference from earliest group significant at $P < .05$. † Difference from earliest group significant at $P < .02$. ‡ Difference from earliest group significant at $P < .02$.

grow more rapidly and for a longer interval. Late maturers are necessarily lighter at age 18 since they are the same mean weight at menarche as early maturers and grow more slowly.

The large coefficients of variability for mean weight for all subjects at maximum rate of growth and menarche, 15.1 percent and 14.4 percent, respectively, compared to 7.5 percent for the mean weight for all subjects at the initiation of the spurt, indicate that other factors may be involved once the spurt has started. However, if the mean weights at maximum rate of growth and menarche are taken to represent metabolic mass, much of the variability around the mean weights could be explained by differences in fat and skeletal structure.

The unchanging mean weight at initiation of the spurt, maximum rate of growth, and at menarche in early and late maturing girls suggests that the attainment of a critical weight may be essential for each of these events of adolescence. A possible mechanism for an interaction of this kind in the rat had been suggested by Kennedy and Mitra to explain their finding of the influence of body size and food intake on the "onset of puberty" in the rat (*11*). Our adaptation of this mechanism to explain menarche proposed (*2*) that attainment of a body weight in the critical range causes a change in metabolic rate, which, in turn, reduces the sensitivity of the hypothalamus to estrogen, thus altering the ovarian-hypothalamus feedback. A mechanism of this kind could operate at different levels (and affect different hormonal systems) at the time of maximum rate of growth and menarche. A change to a critical metabolic rate triggering an increase of growth hormone or androgens or both, or removing an inhibition on output of growth hormone (*12*) could explain the initiation of the adolescent growth spurt.

Although these proposed mechanisms are speculative, some related data seem to support the critical weight hypothesis. The average metabolic rate of girls and boys, computed from Talbot's standards (*13*) for their respective mean weights at the time of maximum rate of growth, is the same, 3.1 cal/kg per day, although the mean weight for girls is about 39 kg at the time of maximum rate of growth, while that of boys is about 47 kg, and their maximum rate of growth in weight on the average occurs 2 years later than that of the girls (*2*). Similarly, at the initiation of the adolescent spurt in weight growth, the average metabolic rate is 3.5 cal/kg per day for both girls and boys, although the mean weight of boys at initiation of the spurt is 6 kg greater than that of the girls and the average time of initiation is 2 years later (*1*).

Significant also are observations about populations at high altitudes; birth weight is lower because of fetal hypoxia (*14*), and menarche is later (*15*) than at sea level. Both these effects were found when the data from the Child Research Council (CRC), Denver, Colorado (1610 m), were compared to the data of the Berkeley Guidance Council (BGS) (sea level). (Both groups of girls are upper middle-class and well nourished; both sets of data were collected from 1930 to 1950.) The mean birth weight of the Denver girls was 3.19 ± .06 kg, their mean age of menarche 13.1 ± .12 years (*16*); the mean birth weight of the Berkeley girls was 3.42 ± .05 kg, their mean age of menarche 12.8 ± .14 years.

Altitude apparently depresses not only birth weight but growth rate after birth (*17*). At age 6, before any subject initiated the adolescent spurt, the mean weight of the Denver girls, 20.30 ± .31 kg, was significantly ($P < .01$) lighter than that of the Berkeley girls, 22.0 ± .36 kg. The Denver girls initiated the spurt in weight growth, attained maximum rate of growth in weight, and reached menarche later than the Berkeley girls by 6.0 ± 2.5, 3.6 ± 2.3, and 3.6 ± 2.2 months, respectively (*16*). But the mean weights of the Denver and Berkeley girls at each of these events did not differ significantly: they were 30.9 ± .49 and 31.5 ± .57 kg, respectively; 39.3 ± .74 and 40.4 ± .68 kg, respectively; and 47.5 ± .85 and 49.4 ± .87 kg, respectively.

These observations fit our hypothesis: since the Denver girls are born smaller and then grow at slower rates, they attain the critical weights at initiation of the spurt, maximum rate of growth in weight, and menarche at a later age.

We have pointed out (*2*) that the well-established secular trend to an earlier menarche (*18*, *19*) is most simply explained by an interaction between size at time of maximum rate of growth in weight and menarche, such as suggested above, since children are bigger earlier (*18*) and thus attain the critical weights earlier.

Comparison of the weights of girls at menarche now with the estimate of 48 kg for two or three decades ago would test the critical weight-menarche hypothesis and the proposed explanation of the secular trend. Both would be supported if the mean weight at menarche has not changed, while the age of menarche has become earlier. The simple measurement of weight of menarche could be obtained directly in prospective studies of menarche and ongoing growth studies.

ROSE E. FRISCH
ROGER REVELLE
Harvard Center for Population Studies, Cambridge, Massachusetts 02138

References and Notes

1. R. E. Frisch and R. Revelle, *Hum. Biol.*, in press.
2. ———, *ibid.* **41**, 536 (1969).
3. The Child Research Council Study (CRC), 64 girls and 76 boys, through the courtesy of Drs. R. McCammon and C. Hansman, University of Colorado, Medical Center, Denver, Colorado; Longitudinal Studies of Child Health and Development, Harvard School of Public Health (HSPH), 67 girls and 67 boys, through the courtesy of Drs. I. Valadian and R. Reed, Harvard School of Public Health; Berkeley Guidance Study (BGS), 70 girls and 66 boys, published in entirety by R. Tuddenham and M. M. Snyder [*Univ. Calif. Publ. Child Dev.* **1** 2, 183 (1954)]. The data are comparable: all three were collected in the years from 1929 to 1950, and the economic status of the parents was average (HSPH) and above average (CRC and BGS).
4. An early maturer initiates the spurt, attains peak velocity, and has menarche in the years before that of the respective mean ages of these events, a late maturer in the years after that of the mean age. For example, the mean age of menarche for all girls of the three studies is 12.9 ± .09 years; an early maturer has menarche at 11.5 years, a late maturer at 14.5 years.
5. Many references cited in J. M. Tanner,

Growth at Adolescence (Blackwell, Oxford, ed. 2, 1962), pp. 96–102.
6. Age of menarche was recorded to the tenth of a year in the CRC and BGS Studies and in months in the HSPH Study; the latter were converted to years and tenths of a year. Height and weight data were given for half yearly (CRC and BGS) and yearly (HSPH, after age 11) intervals. Height and weight at menarche were found by interpolation. Interpolation was within a half year for 71 percent of the girls, within a year for the remainder. Three dates of menarche were missing. Fourteen girls were discarded (12, HSPH; 2, CRC) because of growth data intervals greater than a year at the menarcheal year. The means of age of menarche and height and weight at age 18 of the discarded girls did not differ from those remaining in the study. Three girls (2, BGS; 1, HSPH) with weights at menarche greater than 70 kg, which a study of the distribution of menarcheal weights showed to be clearly abnormal, were omitted.
7. F. K. Shuttleworth, *Monogr. Soc. Res. Child Develop.* **2**, No. 5 (1937).
8. F. K. Shuttleworth, *ibid.* **4**, No. 3 (1939); K. Simmons and W. W. Greulich, *J. Pediat.* **22**, 518 (1943).
9. W. A. Marshall and J. M. Tanner, *Arch. Dis. Childhood* **44**, 291 (1969).
10. F. Boas, *Hum. Biol.* **4**, 307 (1932); H. Richey, *Monogr. Soc. Res. Child Develop.* **2**, No. 1 (1937).
11. G. C. Kennedy and J. Mitra, *J. Physiol.* **166**, 408 (1963).
12. L. Martin, J. W. Clark, T. Connor, *J. Clin. Endocrinol. Metab.* **2**, 425 (1968).
13. F. B. Talbot, *Amer. J. Dis. Child.* **55**, 455 (1938).
14. J. McClung, *Effects of High Altitude on Human Birth* (Harvard Univ. Press, Cambridge, 1969); D. Grahn and J. Kratchman, *Amer. J. Hum. Gen.* **15**, 329 (1963).
15. J. A. Valsik, *Hum. Biol.* **37**, 75 (1965); ———, *Biotypologie* **24**, 109 (1963).
16. R. McCammon [*Amer. J. Pub. Health* **55**, 103 (1965)] gives the mean age of menarche as 13.17 years for the continuing study of CRC girls, making the difference from the Berkeley girls 4.8 months; A. Damon, S. T. Damon, R. B. Reed and I. Valadian [*Hum. Biol.* **41**, 161 (1969)] suggested that the late menarche of the Denver girls and their absence of secular trend "could result in part from altitude."
17. The CRC girls are shorter and weigh less than the BGS girls at every age up to 17 years. At that age they have caught up in height but not in weight.
18. J. M. Tanner, *Tijdschr. Soc. Geneesk.* **44**, 524 (1966).
19. W. A. Marshall and J. M. Tanner, *Ann. Rev. Med.* **19**, 283 (1968).
20. We thank Mrs. S. Cook for her assistance with the statistical computations.

15 April 1970; revised 1 June 1970 ■

Interanimal "Memory" Transfer: Results from Brain and Liver Homogenates

Abstract. *Sixty mice received either shock or no shock in a shuttle box, or nonspecific stress in another apparatus. Brain and liver homogenates from these animals were then injected into 120 naive recipients, who were all tested in the shuttle box. Subjects receiving brain or liver from shocked or stressed donors had significantly higher latencies than control counterparts. These results are interpreted in terms of stress, rather than a memory transfer hypothesis.*

Babich *et al.* (*1*) found that RNA extracts taken from the brains of trained donors and injected into naive recipients facilitated performance of the latter when compared to animals receiving homogenates from untrained donors. This was interpreted as a demonstration of memory transfer. In the many attempts to replicate these results, there have been reports of both successes (*2*) and failures (*3*). This raises a question about the validity of the original interpretation. The discrepancy between successful and unsuccessful replications may involve the type of task used in each; "successes" have frequently employed passive avoidance tasks, and "failures" generally employed positive reinforcement situations. In the avoidance task, an increase in latency of recipients when compared with those of donors is taken as evidence of interanimal memory transfer. But such changes in latency could be the result of performance variables completely unrelated to learning, such as increased emotionality, fatigue, or stressful side effects of the particular experimental procedure. Thus, while these variables may have a pronounced effect on latencies, they may have only a marginal effect on either trials to criterion or error scores, the most common dependent measures in positive reinforcement tasks. These uncontrolled variables could account for the ambiguous results in the literature and raise the issue of whether the results of Babich *et al.*, and others, were due to (i) a specific memory transfer, possibly involving mediation by RNA (*4*) or large protein molecules (*5*), or (ii) the transfer of some factor affecting performance (*6*), such as stress. The present experiments were designed to separate these possibilities by contrasting the hypothesis that memory can be transferred from a trained to an untrained animal, with the hypothesis that "apparent" interanimal transfer in an aversive situation is mediated by nonspecific stress substances.

The subjects were 180 male albino mice, of the CD1 strain from the Charles River Laboratories, weighing 25 to 30 g. The subjects were divided into three groups, each comprised of 20 donors and 40 recipients. Each donor was randomly assigned to two recipients, one for brain homogenate and one for liver homogenate. The liver injection served to provide high concentrations of nonspecific RNA, and also to control for volume of foreign matter injected into the intraperitoneal cavity.

The behavioral apparatus was a rectangular box, 42.5 by 12 by 11 cm, one half of which was painted white and the other black, with the two sections separated by a center partition. The floor consisted of a grid of 0.2 by 12 cm brass rods placed 0.3 cm apart. The black side had a removable opaque cover, and the white side was illuminated with a high-intensity lamp producing 3300 lu/m^2 at the top of the box. The dependent variable for the donors was the number of seconds the subjects took to enter the black section from the white section through an opening in the center partition. Each donor was given only one trial in the apparatus, after which the maze was first cleaned with "Windex" spray containing ammonia and then distilled water to remove any odor-producing steroids which might affect subsequent animals. On the basis of previous research, all prospective donors taking longer than 30 seconds to enter the black section were discarded as atypical (this amounted to five animals across all three groups).

The shock-group donors received 5 seconds of scrambled shock (1.2 ma a-c) after entry into the black section of the box. The procedure for donors in the no-shock group was identical to that of shocked donors except that the former were not shocked while detained in the black section.

The stressed, control donors were placed in a ventilated glass jar, 5.5 cm in diameter and 7 cm tall, and rolled back and forth five times across a distance of approximately 15 cm.

Immediately following the procedures described above, each donor was decapitated, and the brain and liver quickly removed, weighed, and individually homogenized with an equal weight of distilled water. The entire liver was used in that homogenate, whereas the brain preparation did not include the olfactory bulbs and the cranial nerves. Next, a single injection of either brain or liver substance was given intraperitoneally in the upper left abdominal area of the appropriate recipient, who was first lightly anesthetized with ether to reduce pain. The volumes of the two