## Metabolism of Catechol Estrogens by Erythrocyte Catechol-*O* Methyltransferase

Fishman and Tulchinsky (*1*) present evidence that the catechol estrogen 2-hydroxyestrone suppresses serum prolactin in normal ovulatory young women. However, in 3 of the 12 subjects studied the authors were unable to suppress serum prolactin and suggested that prolactin response to 2-hydroxyestrone is subject- and not time-dependent.

In a study designed to evaluate the kinetics of catechol estrogen formation from plasma estrone in vivo, Bates *et al.* (*2*) were unable to compute the transfer constant of conversion of estrone to 2-hydroxyestrone because of intravascular metabolism of 2-hydroxyestrone by erythrocytes. During the infusion, the radioactively labeled 2-hydroxyestrone was metabolized to its methyl ether, 2-methoxyestrone, by erythrocyte catechol-*O*-methyltransferase (COMT). This finding led to the development of a radioenzymatic assay for quantifying COMT in erythrocytes with the use of radioactively labeled 2-hydroxyestrone as the substrate (*3*).

Weinshilboum *et al.* (*4*) have demonstrated a bimodal distribution of COMT activity in erythrocytes from 373 randomly selected young men and women. We have not identified a bimodal distribution of COMT activity in our investigations, but we have found increased COMT activity in erythrocytes of pregnant women (*5*), in women with pregnancy-induced hypertension, and in fetal blood (*6*).

We suggest that the three subjects studied by Fishman and Tulchinsky who failed to have prolactin suppression may have increased erythrocyte COMT activity. This could result in intravascular metabolism of 2-hydroxyestrone before the infused material reached its site of action. We further suggest that measurement of erythrocyte COMT activity should be part of the investigation of catechol estrogen infusion studies.

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## Duration of Preschool Effects on Later School Competence

Darlington and colleagues (*1*) report that children who had attended infant and preschool programs had significantly higher rates of meeting school requirements (defined as not being held back a grade or placed in special education) than did controls. They also report that IQ measures taken on the same subjects showed large initial gains that had vanished 5 years after the completion of preschool. They made no attempt, however, to see whether preschool effects on school performance also diminished over time. Consequently, readers are left with the impression that, unlike the results for IQ, preschool effects on measures of school performance were permanent.

Separating the studies analyzed by Darlington *et al.* into two groups according to grade at follow-up (Table 1) reveals that there is no significant effect of early enrichment beyond elementary school. The pooled $z$ (*2*) for the four studies where follow-up took place in junior or senior high school is only 1.62 (pooled $P > .1$), whereas for the three studies with follow-up in elementary grades it is 3.6 (pooled $P < .001$). Darlington's test for the robustness of any finding was to delete the strongest result from a group of studies. When this test is applied to the follow-up of older children, the small preschool effect almost vanishes (pooled $z = .29$, pooled $P > .75$). Thus the beneficial effects of preschool on school performance (as defined by Darlington *et al.*) were no more durable than the preschool effects on IQ.

Concerning the effect on elementary school children, there is a possible source of confounding: teacher's knowledge of preschool attendance. The decision to retain a child in a grade or send him or her to special education might have been influenced by knowledge that the child had or had not already been given special training. If information about preschool attendance was part of the child's elementary school record, this effect might have been substantial, in which case what was measured by the variables chosen was not necessarily differences in school competence.

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### References and Notes

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2. The method specified by Darlington *et al.* in their reference 10 (*1*) was used for these calculations.

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Table 1. Comparison of treatment and control groups on failure to meet school requirements. [Data from table 2 in (*1*)]

| Grade | Project | $N$ | Failed to meet requirements (%) | | $P$ (two-tailed) |
|---|---|---|---|---|---|
| | | | Treatment | Control | |
| | *Follow-up in junior or senior high school* | | | | |
| 12 | Gray | 55 | 52.8 | 68.4 | .263 |
| 12 | Beller | 69 | 45.9 | 50.0 | .737 |
| 7 | Palmer | 221 | 24.1 | 44.7 | .006 |
| 7 | Miller | 125 | 20.6 | 11.1 | .346 |
| | *Follow-up in elementary grades* | | | | |
| 5 | Gordon | 82 | 39.1 | 61.5 | .134 |
| 4 | Weikart | 123 | 17.2 | 38.5 | .009 |
| 3 | Levenstein | 127 | 22.1 | 43.5 | .035 |

Our report (*1*) presented data from a continuing study by the Consortium for Longitudinal Studies. The consortium members have since provided us with data past elementary school for all seven projects in Horn's table 1 (although the dependent variable for the Weikart project is placement in special education classes rather than a more general measure of failure to meet school requirements). These newer data yield a highly significant result (pooled $z = 3.55$, $P = .0004$) which is robust after deletion of the most significant single result (pooled $z = 2.68$, $P = .0074$). Thus there is no indication that effects last only through elementary school.


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The data from the later follow-up are also relevant to Horn's hypothesis that teachers are less likely to retain in grade or place in special classes children whom they know were in preschool programs. If this effect existed, presumably it would occur primarily in grades 1 and 2, so that the difference between treatment and control groups should be especially large at that time. Just the opposite was found; there were no significant differences in the first two grades (pooled $z = .02$, $P = .98$ at the end of grade 1; pooled $z = .92$, $P = .36$ at the end of grade 2). For all projects combined, at the end of the second grade the proportion of children classified as failing to meet school requirements was 39/515 (7.6 percent) in the treatment groups and 23/234 (9.8 percent) in the control groups. We plan to report those results in more detail in future publications.

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## Preventing Maternal Cannibalism in Rats

The elaborate procedures described by Libbin and Person (*1*) to reduce or prevent maternal cannibalism in rats are, in my experience, generally unnecessary. In my experiments on pregnant rats, the animals are received 3 days after mating and housed in hanging solid-bottom cages measuring 24 by 40 by 17.5 cm in a room with a 12-hour light-dark cycle (light is provided by overhead fluorescent bulbs). This lighting regimen is maintained throughout pregnancy and lactation. No attempt is made to reduce the amount of light entering the cages.

There is a thin (~ 1 cm) layer of wood shavings on the floor of each cage. Twice weekly the rats are removed from the cages long enough for the fouled shavings to be removed and replaced with clean shavings. If the shavings are not changed within 30 days, the accumulation of excess urine and feces leads to the production of ammonia, which may produce lung lesions in the mothers and pups. Failure to change the shavings for 30 days also violates guidelines established by the National Institutes of Health (*2*) and could result in the loss of accreditation of the laboratory by the American Association for Accreditation of Laboratory Animal Care.

The extensive "hand gentling" described by Libbin and Person is not necessary to prevent maternal cannibalism. I have conducted experiments in which the mothers are either weighed three times per week (*3*) or weighed only on arrival and not disturbed further until parturition (*4*). At birth the pups are removed from the mothers, pooled, randomly assigned to other mothers, removed again, weighed, injected with drugs, and returned to the surrogate mothers (*4*) with virtually no resulting cannibalism. The pups can be weighed one to three times weekly throughout the nursing period, as needed. All these procedures involve routine handling similar to what nonpregnant or nonlactating rats receive. I did not observe that "merely handling pups, as in the carrying out of simple injection procedures, produces [cannibalism]" (*1*). In fact, cleaning the cages, weighing the mothers and pups, and manipulating the pups experimentally may serve the same purpose as "hand gentling."

Cannibalism does occur in laboratory rats, but is generally restricted to the consumption of stillborn pups or pups weakened or dead as a result of experimentation. Usually there is a 12- to 24-hour interval between death of the pup and its consumption by the mother.

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## Microencapsulated Islets in Diabetic Rats

In discussing briefly in our report (*1*) some techniques used to circumvent the problem of the immune rejection of islets, we incorrectly referred to Sutherland *et al.* (*2*) as injecting neonatal rats with DL-ethionine to prevent rejection. In fact, Sutherland *et al.* treated adult rats with DL-ethionine only as an adjunct to the preparation of islet tissue. In our statement on Mullen *et al.* (*3*) we should have said that these workers used fetal pancreas in an attempt to avoid rejection and cited an additonal reference (*4*). Further, it has been pointed out (*5*) that the term allotransplantation would have been more appropriate than isotransplantation in describing our experiments (*6*).

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