nuclear material and the cytoplasm is undegraded IAA-C^{14} or 2,4-D-C^{14}, the fact that both give the same labeling pattern may suggest that degradation is not involved.

Our positive results could be regarded as due to some nonselective binding of 2,4-D-C^{14} or IAA-C^{14} to the cellular components or to some artifact during preparation. However, these results seem to indicate some physiological significance, since only certain meristematic cells acquire most of the label, and control preparations of root tips not exposed to radioactive IAA or 2,4-D cause no detectable labeling above the background on the film.

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Phenylalanine: Transplacental Concentrations in Rhesus Monkeys

Abstract. *Amino acids are actively transported across the mammalian placenta, with concentrations in fetal blood being higher than those in the maternal circulation. Elevated concentrations of phenylalanine were induced by dietary means in the blood of pregnant rhesus monkeys, and the active transport mechanism was evident at both normal and elevated concentrations. A normal placental process may thus magnify a maternal biochemical abnormality and produce a more profound disturbance in the fetus.*

The mechanism responsible for mental retardation in phenylketonuria is unknown, but is associated with high concentration of phenylalanine in the blood. Recent reports indicate that infants born to mothers having phenylketonuria may be retarded without measurable abnormality in phenylalanine metabolism (*1*); they suggest that an elevated concentration of phenylalanine in the maternal blood may cross the placenta and in some way damage the fetal brain. We have evaluated this hypothesis by measuring maternal and fetal blood concentrations of phenylalanine (*2*) in full-term pregnancies in the rhesus monkey.

Female monkeys were mated and the dates of conception were established; all were individually caged and records were kept of dietary intake, weight, and clinical status. In eight control pregnancies the animals were fed commercial chow, milk, vitamins, and fruit. Infants were separated from mothers from the moment of birth. From simultaneous blood specimens from the mother and from the umbilical cord of her infant were determined the normal free amino acid concentrations (*3*); two sets of maternal and cord specimens were obtained at the time of elective cesarean section.

In six other pregnancies the maternal diet was supplemented with excess L-phenylalanine in amounts ranging from 0.2 to 1.4 g day^{-1} per kilogram of body weight, which was added to commercial milk which, with vitamins and fruit, provided the total nutrition. In order to maintain a constant elevation of serum phenylalanine it was necessary to feed the supplemented milk at 4-hour intervals (*4*). Serum phenylalanine was determined at biweekly intervals during the pregnancy, each blood specimen being obtained 4 hours after the previous dietary intake. After birth, maternal and cord-blood specimens were analyzed for all free amino acids. In two pregnancies, cord blood was unobtainable and a specimen of the infant's peripheral blood was collected within 5 minutes of birth.

In control pregnancies the cord:maternal ratio (C:M) was greater than unity for all amino acids. The mean serum concentrations of phenylalanine in mother and cord were 1.26 and 1.67 mg/100 ml, respectively; the mean C:M for phenylalanine was 1.49 (Table 1).

Females fed the phenylalanine-supplemented diet had mean concentrations of phenylalanine in serum, during pregnancy, ranging from 14.7 to 40.4 mg/100 ml. One pregnancy resulted in death of the fetus because of its abnormal position at the time of birth. A second mother refused to eat and became dehydrated during the last 2 days of pregnancy; both maternal and cord serums in this pair revealed generalized hyperaminoacidemia.

The four other females whose diets were phenylalanine-supplemented produced clinically normal infants at full-term pregnancy. Signs of nutritional or neurologic damage were not detected in any infant. The concentration of phenylalanine in the serums of mothers

Table 1. Transplacental concentrations of phenylalanine and tyrosine in serums and cord:maternal ratios (C:M) in four mother-fetus couples.

Phenylalanine (mg/100 ml)			Tyrosine (mg/100 ml)		
Cord	Mother	C:M	Cord	Mother	C:M
Pregnant mother's diet supplemented with phenylalanine					
45.3	22.0	2.06	11.2	7.5	1.49
43.1	11.8	3.65	13.7	4.6	2.98
43.7	27.2	1.61	11.9	6.3	1.61
12.88	6.99	1.84	4.09	2.41	1.70
Eight controls (average)					
1.68 ± 0.28	1.26 ± 0.49	1.49 ± 0.58	1.46 ± 0.33	0.93 ± 0.29	1.66 ± 0.56

was from 11.8 to 27.2 mg/100 ml at delivery, but the concentration in corresponding cord or infant was always higher (Table 1).

Although the data from pregnancy 2 suggest that an elevated concentration of phenylalanine in blood may alter normal placental mechanisms and produce a C:M higher than that shown by control pregnancies, the number of animals studied prevents any conclusion on this point. Notably, however, the elevated concentrations of phenylalanine in umbilical cords in the other three pregnancies were produced by a placental transport process that showed a normal C:M.

With the exception of tyrosine, all concentrations of other amino acids and all C:M's were within the control range. The increased concentration of tyrosine in both maternal and cord serums indicates a normal hepatic enzyme system for hydroxylating phenylalanine. Whether the elevated concentration of tyrosine in fetuses reflects an induced fetal hydroxylating system, or whether it reflects active placental transport of the elevated maternal concentration of tyrosine, we cannot now determine. It is apparent, however, that the C:M for tyrosine is similarly within the control range.

The mechanism whereby higher concentrations of amino acids are maintained in blood of the mammalian fetus than in the mother implicates an active transport process and is specific for the L-isomers (*5*); its basis is unknown, and it may reflect either increased need for amino acids to provide the substrates for protein synthesis in fetuses, or a deficiency of the enzymes required for fetal metabolism of amino acids. Elevated C:M's have been most evident in immature or premature human fetuses (*6*), and it is therefore likely that the fetuses in this study were exposed to even higher phenylalanine concentrations in blood than were demonstrated at full-term delivery.

This "concentrating" ability of the placenta has not been considered heretofore to represent a potential threat to the fetus. Boggs and Waisman, however, noted that fetuses of rats fed a phenylalanine-supplemented diet had higher phenylalanine concentrations in plasma than their mothers (*7*); we have subsequently shown the same phenomenon with histidine, tyrosine, and tryptophan. Our data demonstrate that this primate placenta functions similarly, and not only concentrates a normal maternal serum level of phenylalanine, presumably for the benefit of the fetus, but also concentrates an elevated maternal level, perhaps to fetal detriment.

Children with phenylketonuria have normal phenylalanine concentrations in plasma at birth (*8*), which fact indicates that the placenta protects the developing fetus from the consequences of its own metabolic defect. The observation that females having phenylketonuria may bear children who are retarded, without themselves having the disorder, suggests that the fetus is damaged *in utero* by some expression of the maternal disease, presumably the elevated concentration of phenylalanine. Our data indicate that in such pregnancies the placenta, by performing its normal function, may expose the fetal brain to added insult by magnifying the maternal biochemical abnormality. The infant monkeys born to these phenylalanine-supplemented mothers have been raised under standard laboratory conditions since birth, and their physical growth has been well within the normal range. They are being studied for possible abnormality in learning or social behavior; object-discrimination trials, the first of a battery of learning tests (*4*), indicate that the three infants tested so far perform not significantly differently from control animals.

A wide variety of drugs, biochemicals, and minerals, as well as amino acids, reach higher concentrations in fetal blood and tissues than in the mother (*9*). Whether the active placental transport processes for any of these persist in the presence of an elevated maternal concentration remains to be investigated, but our data may help to explain how a biochemcal disturbance in the pregnant female may have a more profound effect on her developing fetus.

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Catecholamine Concentrations: Changes in Plasma of Rats during Estrous Cycle and Pregnancy

Abstract. *Concentrations of norepinephrine in plasma of rats during estrus and pregnancy were significantly lower than during diestrus. Epinephrine concentrations in the plasma were significantly higher in both estrous and diestrous females than in males.*

The catecholamine content of the uterus of the rat was reported to vary with the state of estrus of the animal (*1*). Both concentration and quantity of epinephrine per uterus were low during diestrus and increased with estrus. Norepinephrine content per uterus did not change under these conditions, although the concentration decreased as the weight of the uterus increased during estrus. Changes in the catecholamine content of the uterus in rabbits and humans during various endocrine states have also been noted (*2*). Alterations of either biosynthesis of epinephrine (*3*) or uterine blood flow (*4*) could not adequately explain the cyclic variations noted. On the basis of a study of the kinetics of transport of catecholamines into the uterus in vitro, Green and Miller (*5*) postulated that small changes in the ratio of epineph-