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-

Table 1. Concentrations of catecholamines in the plasma of rats.

Sex or state; No. of samples	Concentration ± SE (μg liter^{-1})	
	Norepinephrine	Epinephrine
Male, 6	0.73 ± 0.16	1.38 ± 0.15*
Estrus, 7	0.44 ± 0.05†	2.74 ± 0.39
Diestrus, 5	1.14 ± 0.24	1.98 ± 0.13
Metestrus, 4	1.08 ± 0.25	2.17 ± 0.56
Pregnant, 8	0.26 ± 0.13‡	2.33 ± 0.10

* Statistically different from estrus, diestrus, and pregnancy, $P < .05$. † Statistically different from diestrus, $P < .05$. ‡ Statistically different from metestrus, diestrus, and male, $P < .05$.

rine to norepinephrine in the plasma could alter the relative uptake of these two amines by the uterus and thus change the relative amounts in the uterus. Our purpose was to determine whether changes in the concentrations of epinephrine and norepinephrine in the plasma of rats during the estrous cycle and pregnancy occur in a manner consistent with this hypothesis.

Adult male and female Simonsen rats, weighing 200 to 250 g, were used; all were anesthetized with pentobarbital sodium at 30 mg kg^{-1}. The state of estrus was determined by microscopic examination of vaginal washings from the nonpregnant females. Following laparotomy, 4 to 5 ml of blood was withdrawn from the abdominal aorta into a syringe previously rinsed with heparin; blood from three to four animals was pooled for each sample, and plasma catecholamines were assayed (*6*).

Concentrations of epinephrine and norepinephrine in plasma from male, estrous, diestrous, metestrous, and pregnant rats are listed in Table 1. The important differences may be summarized as follows: (i) the concentration of norepinephrine in plasma from estrous and pregnant animals was significantly lower than from diestrous animals, (ii) the concentration of epinephrine in plasma from estrous and diestrous females was statistically greater than from males, and (iii) epinephrine was of greater concentration than norepinephrine in the plasma of all groups tested.

Published data on uterine concentrations of catecholamine (*1, 3, 7*) led us to two correlations of interest: The concentration in tissue of epinephrine or norepinephrine was directly proportional to the concentration of the particular amine in the plasma; and, as the ratio of epinephrine to norepinephrine in the plasma increased, the percentage of total uterine catecholamines, represented by epinephrine, also increased. These correlations, along with the data presented, are consistent with the hypothesis that the cyclic variations in uterine catecholamines observed in the rat result from variations in the ratio of epinephrine to norepinephrine in the plasma and in the transport of these amines into the uterus.

In all groups studied the mean epinephrine concentration was higher than the corresponding norepinephrine concentration. In most species the concentration of norepinephrine exceeds that of epinephrine (*6*). It could be argued that the epinephrine values reported in Table 1 were elevated because of adrenal-gland discharge caused by the blood-sampling procedure employed. Stern and Brody (*8*) reported values for the epinephrine and norepinephrine concentrations in plasma from female rats during hexobarbital anesthesia; their blood samples came from the inferior vena cava. Their values were similar to the diestrous-plasma values shown in Table 1, although the epinephrine concentration was somewhat lower. Rubinstein (*9*) also reported epinephrine values in rat plasma; he obtained blood samples, by cardiac puncture, from males under pentobarbital anesthesia; his animals were acutely adrenalectomized just before the cardiac-puncture procedure. His average epinephrine concentration in plasma was essentially the same as that for the male group listed in Table 1. Thus the values reported from our study are in close agreement with values reported in the literature and obtained by use of the trihydroxyindole procedure. There are indications that these values were not due to excessive discharge of the adrenal gland although the extent of discharge is unknown. Much higher values than those just considered were reported by Anton and Sayre (*6*), who indicated that their value for epinephrine was possibly due to adrenal discharge. The finding that the epinephrine concentration in plasma was higher in females than in males agrees with an earlier finding in humans (*10*). Catecholamine concentrations in the circulation also were reported to vary during human pregnancy (*11*).

The finding that the epinephrine content (relative to body weight) of the adrenal glands was higher in female rats than in males (*12*) may relate to the sex difference noted in our study for the concentrations of this amine in plasma. While the variations in catecholamines in plasma appear to correlate well with their concentrations in the uterus, the findings may also have more general significance.

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Environmental Control of Ovarian Development in Mosquitoes of the Culex pipiens Complex

Abstract. *Gonotrophic dissociation, a condition in which the ovaries remain undeveloped in female mosquitoes that have taken a full blood meal, occurs in* Culex pipiens *L., when incubated at low temperature (10° to 15°C) with short photoperiod and held at low temperature after feeding. Gonotrophic dissociation occurred sporadically in* Culex quinquefasciatus *Say after conditioning by low temperature, irrespective of photoperiod. Two major considerations are posed: first, the importance of gonotrophic dissociation to hibernation potential; and, second, the potential of a hibernating female mosquito to serve as a virus reservoir.*

The term gonotrophic dissociation (*1*) is commonly applied to any situation where the ovaries remain undeveloped in female mosquitoes that have taken a full blood meal. Although gonotrophic dissociation in this sense has been reported as occurring in members of the *Culex pipiens* complex from