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Plasma Unesterified Fatty Acid Concentration in Fetal and Neonatal Life.* (25330)

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During late stages of pregnancy the human fetus rapidly builds up fat stores in adipose tissue. High respiratory quotients during this period suggest catabolism of carbohydrate or synthesis of fat, or both(1). Decrease in respiratory quotient to approximately 0.7(2) and loss of weight usually seen in first few days of life suggest that these lipid stores are drawn on for energy needs in neonatal life. Utilization of lipid is not surprising since glycogen stores are not overly abundant in the newborn(2) and since protein catabolism can account for only a fraction of caloric requirement during first 48 hours of life(3). Recent studies on metabolic activity and physiological significance of plasma unesterified fatty acids (UFA) in adult mammals indicate that UFA originate chiefly in adipose tissue and appear to be the major form of transported lipid immediately available for oxidation by peripheral tissues(4). The plasma level of UFA is decreased under conditions that promote oxidation of carbohydrate, and increased when carbohydrate is less readily available for energy needs(4). These considerations led us to investigate metabolism of UFA in fetal and neonatal life. Our report describes plasma levels of UFA in sheep fetus and in newborn man and sheep during first few hours of life. Plasma UFA concentrations in mothers were also measured concomitantly.

Methods. Studies in sheep. In sheep the uterus can be opened and umbilical vessels cannulated without apparent disturbance of the placental function(5). Cesarean sections under chloralose anesthesia were performed on 4 crossbred sheep within a few days of term. The fetuses were delivered and immediately immersed without interruption of placental circulation in bath of Ringer's solution maintained at 39°C. Polyethylene catheters were placed in tributaries of the umbilical artery and vein and threaded into main channels. A catheter was also placed in carotid artery of the mother. Serial blood samples were obtained simultaneously from these 3 sources over 1 to 3 hr. period. In one case the fetus was delivered successfully from the incubating bath and serial blood samples were obtained from the umbilical artery for 6 hours. *Studies in man.* Mothers of infants received a variety of analgesic and anesthetic agents during labor. Single blood samples were obtained from the umbilical vein and artery of 9 newborn infants and from an antecubital vein of their mothers. All samples were taken within 2 min. after delivery and before separation of the placenta (Group 1). In an additional 8 cases, samples were taken from either the umbilical vein or artery of the infant and from the antecubital vein of the mother 1 to 7 min. after delivery (Group 2). Single blood samples were also obtained from the internal jugular vein of 9 newborn infants 1 to 6½ hr after birth (Group 3).§ These samples were

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§ We are indebted to Dr. William Tooley for obtaining these samples. In adults we found (unpublished) that UFA concentrations of internal jugular and arterial blood plasma are comparable.

TABLE I. Unesterified Fatty Acid Concentration (UFA) in Fetal and Maternal Blood Plasma of Sheep. (Expressed as mean and range.)

Source	Exp. 1 No. samples	Exp. 1 UFA, μeq/ml	Exp. 2 No. samples	Exp. 2 UFA, μeq/ml	Exp. 3 No. samples	Exp. 3 UFA, μeq/ml	Exp. 4 No. samples	Exp. 4 UFA, μeq/ml
Umbilical vein	8	.14 (.10- .18)	7	.12 (.10-.15)	4	.12 (.08-.20)	4*	.13
Umbilical artery	8	.15 (.10- .23)	9	.12 (.08-.18)	4	.15 (.08-.26)	4*	.14
Maternal artery	10	1.14 (.98-1.32)	15	.42 (.30-.63)	6	.38 (.26-.52)	9	1.0 (.82-1.12)

* Pooled samples.

obtained within 5 min. of taking the infant from the crib. In an additional 2 infants single blood samples were obtained from femoral vein 6 hr after delivery. The infants received no nutrients prior to blood sampling. *Analytical.* All blood samples were mixed with 1.5 mg/ml of sodium oxalate, chilled in ice and centrifuged at 4°C. Plasma was analyzed immediately or stored at –19°C. UFA were extracted from plasma by the method of Davis(6). Ether extracts were evaporated under air stream at room temperature, taken up in heptane, and titrated according to the method of Dole(7). Total reducing substances were determined by the method of Somogyi (8) and glucose by the method of Huggett and Nixon(9).

Results. In sheep (Table I). In the fetuses plasma levels of UFA were uniformly low. Since titration values in extracts of fetal plasma frequently did not exceed twice the blank titration value, these results must be considered approximations of the true concentrations. No detectable difference was found between samples obtained from umbilical artrey and vein. Maternal plasma levels of UFA were much higher than fetal levels in all cases, but showed considerable individual variation. In one newborn lamb (Exp. 4, Table I) UFA concentration showed a striking rise, beginning 1 hr after delivery and continuing for 6 hr. Then it had increased tenfold (Fig. 1). During this period the concentration of total reducing substances fell considerably.

In man. As in fetal sheep, plasma levels of UFA were considerably lower in newborn infants in Group 1 than in their mothers (Table II). Comparable levels were obtained in Group 2. In mothers of the latter group the

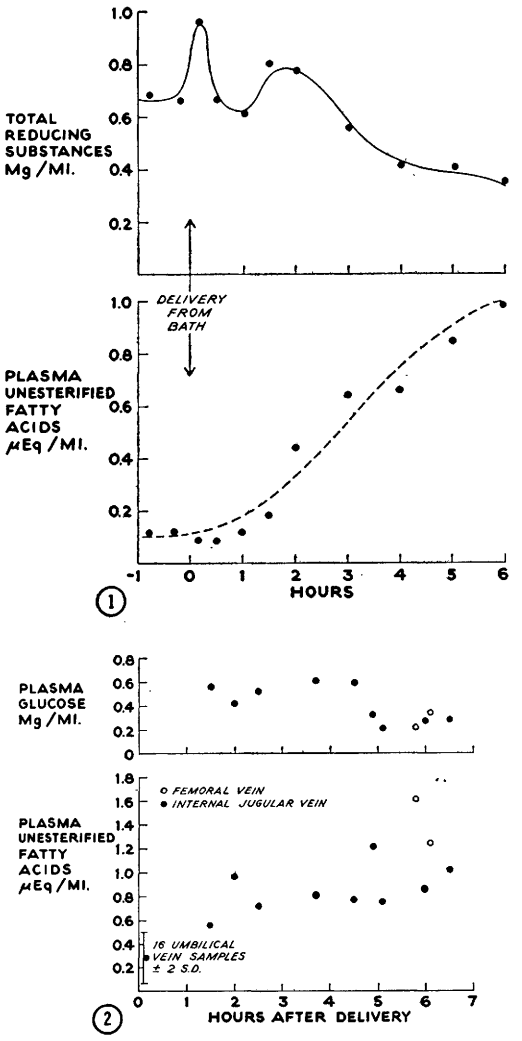

FIG. 1. Changes in the concentration of total reducing substances and UFA in blood plasma of a lamb prior to and after delivery. Nikethamide, 125 mg, was inj. into the umbilical artery at time of delivery.

FIG. 2. Changes in the concentration of glucose and UFA in blood plasma of newborn infants.

TABLE II. Unesterified Fatty Acid Concentrations in Plasma of Newborn Infants and Their Mothers.

Sec. after delivery	Unesterified fatty acids, μeq/ml			Medications and mode of delivery
	Umbilical vein	Umbilical artery	Maternal vein	
10	.20			100 mg pentobarbital
60		.20	.96	Cesarean section
				Spinal anesthesia
30	.26			Diabetic
120		.17	.98	100 mg pentobarbital
				10 mg morphine
				.4 mg scopolamine
				Cesarean section
				Spinal anesthesia
30	.25		.80	75 mg meperidine
120		.10		Vaginal delivery
				Local anesthesia
30	.16			No medication
150		.22	.88	Vaginal delivery
				Local anesthesia
40	.24			200 mg secobarbital
180		.33	.85	Trichloroethylene
				Vaginal delivery
				Local anesthesia
120	.37			50 mg meperidine
180		.26	.90	25 mg promethazene
				Vaginal delivery
				Local anesthesia
120	.50			*Idem*
180		.25	.90	
120	.20			No medication
240		.15	.85	Vaginal delivery
				Local anesthesia
180	.26			100 mg meperidine
300		.26	.98	Vaginal delivery
				No anesthesia
Mean	.27	.22	.90	
S.D.	.11	.07	.06	

highest concentration of UFA (1.38 meq/l) was found in a patient who had completed a prolonged labor. UFA concentration of plasma from the umbilical vein of the infant of this mother, however, was not significantly higher than that of other newborns. UFA concentrations were usually lower in samples obtained from the umbilical artery than from the umbilical vein, but this difference was not statistically significant ($.4>p>.3$).

Plasma UFA concentrations showed no significant change during the first 7 min. of extrauterine life. The levels had risen significantly, however, 2 hr after birth and continued to increase up to 6½ hr. Plasma glucose concentration was low when first measured 1½ hr after birth and was strikingly reduced after 5 to 7 hr (Fig. 2).¶

Discussion. Low plasma levels of UFA in fetal sheep and newborn infants are consistent with the concept that the mammalian fetus obtains the bulk of its energy requirements from catabolism of carbohydrate. The levels in fetal sheep are the lowest noted consistently in any situation yet reported(4). Existence of a large difference in concentration of plasma UFA in the fetal and maternal circulations suggests that the placenta might not be freely permeable to UFA. However, in preliminary studies (unpublished) palmitic acid-1-C^{14} was shown to cross placental membranes in sheep and rabbits rapidly.

¶ Published data indicate that plasma glucose concentration is within normal limits at birth(2).

The increase in plasma UFA concentration during the first few hours after birth strongly suggests that UFA are rapidly mobilized from adipose tissue stores and serve to supply the energy needs of the organism. The associated hypoglycemia points to deficient carbohydrate oxidation as the probable major factor responsible for increased UFA concentration. An increase in sympathetic nervous activity could also account in part for the increase observed during the first few hours of life(10). The influence of various medications administered to mothers during labor cannot be defined fully, but it should be noted that the changes in UFA concentration were consistent in all infants studied.

The results presented raise the question of the effects of possible defective mobilization of UFA on survival of the full-term infant. The premature infant, furthermore, may lack sufficient stores of fat in adipose tissue to supply adequate quantities of UFA to vital organs. Further studies will be required to answer these and other questions raised by this investigation, such as source and fate of plasma UFA in the fetus, factors controlling the plasma level of UFA in the fetus and newborn, and the contribution of UFA to energy metabolism in fetal and neonatal periods.

Summary. Concentration of UFA in blood plasma of fetal sheep and newborn man was consistently much lower than in plasma obtained simultaneously from their mothers. The levels were comparable to those found in man after administration of glucose or insulin. In both species the plasma level of UFA rose rapidly within 2 hr of birth with an associated hypoglycemia. These findings support previous studies which suggested the occurrence of a rapid shift from carbohydrate to fat catabolism in the neonatal period.

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Isolation and Characterization of Glucuronic Acid Conjugates of Chlorpromazine in Human Urine. (25331)

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Salzman and Brodie(1) and independent investigation by this laboratory(2) showed chlorpromazine sulfoxide to be a metabolite of chlorpromazine in the dog and man. Ross, Young and Maass(3,4) reported demethylation of chlorpromazine in the rat, indicating the existence of demethylated products of chlorpromazine and possibly chlorpromazine sulfoxide as metabolic products of chlorpromazine. Walkenstein and Seifter(5) reported the presence of mono-demethylated products of promazine and promazine sulfoxide in urine of dogs treated with promazine. Hydrolysis of dog and human urine by acid, alkali or β-glucuronidase treatment increases the amount of phenothiazine-like extractable material(2, 6). The conjugated material represents a large fraction of chlorpromazine metabolites excreted in the urine. In this study, we have isolated such material from the urine of pa-