# Genesis of fatty liver and hyperlipemia in the fetal guinea pig

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**Abstract** 10 to 20% of [1-$^{14}$C]palmitate injected into pregnant guinea pigs was recovered in lipids of their fetuses. From these data and the rate of transport of palmitate in maternal blood, it appears that placental transport of free fatty acids can account for the accumulation of lipids in late gestational fetuses. About 80% of the labeled palmitate in the fetus appeared initially in lipids of the liver. $^{14}$C appeared in plasma triglyceride fatty acids after a few minutes and subsequently accumulated in lipids of white and brown adipose tissue, suggesting that much of the palmitate deposited in adipose tissue was derived from hepatogenous triglyceride fatty acids. By contrast, $^{14}$C was usually maximal in heart and carcass lipids before it appeared in plasma triglyceride fatty acids. Lipoprotein lipase activity in fetal adipose tissue was low, and activity of cofactor protein of lipoprotein lipase in fetal blood plasma was much lower than that observed in other mammalian species. On the basis of these and earlier observations, it is concluded that the accumulation of triglycerides in liver and blood plasma of fetal guinea pigs during late gestation is at least partly the result of the large uptake of maternally derived free fatty acids by the fetal liver accompanied by rapid synthesis and secretion of triglyceride-rich very low density lipoproteins into the blood. However, limited uptake of triglyceride fatty acids in adipose tissue may contribute to the fatty liver and hyperlipemia.

**Supplementary key words** free fatty acids · triglyceride · very low density lipoproteins · placental transport · adipose tissue · lipoprotein lipase

In an earlier study (1), we observed that the fetal guinea pig develops an extraordinary fatty liver and hyperlipemia near term (70 days) accompanied by morphological evidence of active synthesis and secretion of lipoproteins in the liver. In thin sections from osmium-fixed tissue, the hepatic parenchymal cells were found to contain large quantities of electron-opaque particles clustered in secretory vesicles of the Golgi apparatus; similar particles were concentrated in the adjacent extracellular spaces. Both the particles within the liver and their presumed product VLDL in the plasma were unusually large. The latter had chemical and physical properties resembling those of chylomicrons more than those of hepatogenous VLDL in other species, consisting of approximately 85% by weight of triglycerides. In view of the ease with which FFA cross the placenta of the guinea pig (2, 3), we suggested that they were the precursors of TGFA in the liver and plasma and that the fatty liver and hyperlipemia were accompanied by extensive transport of FFA from mother to fetus. These phenomena could then result from overloading of the pathways for disposal of hepatic TGFA. This postulate has been tested in the present study by evaluating placental transfer and metabolism of isotopically labeled FFA injected into maternal guinea pigs and by comparing the fatty acid compositions of FFA and TGFA in maternal and fetal tissues. Some factors that regulate disposal of plasma triglycerides have also been examined in the fetus.

## METHODS

### Experimental animals

Pregnant guinea pigs obtained from a local vendor were kept for several days at 20°C before use. They had free access to water and food pellets (Berkeley Diet Guinea Pig Food, Foodstuffs Processing Co., San Francisco) containing 20% protein and 4% fat supplemented with lettuce. Fetal age was determined from the mean weight as previously described (1).

### Materials

[1-$^{14}$C]Palmitic acid (60 $\mu$Ci/$\mu$mole), obtained from New England Nuclear Corp., Boston, Mass., was complexed to bovine serum albumin (4) and stored at 4°C. More than 99% of the radioactivity had solubility characteristics of long-chain fatty acids when subjected to the solvent partition method of Borgström (5). Heparin, 100 IU/mg, was obtained from Nutritional Biochemicals Corp.,

Abbreviations: FFA, free fatty acids; TGFA, triglyceride fatty acids; PLFA, phospholipid fatty acids; VLDL, very low density lipoproteins.

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Cleveland, Ohio; bovine serum albumin from Armour Pharmaceutical Co., Chicago, Ill.; and Intralipid triglyceride emulsion, 10%, from Vitrum AB, Stockholm, Sweden.

### Experimental procedure

The techniques for Cesarean section with removal of fetuses in sequence and the sampling of blood have been reported (1). For isotopic experiments, an external jugular vein and an external carotid artery were exposed under Fluothane anesthesia through a midline incision and catheterized with polyethyene tubing (ID, 0.034 inch; PE 90, Clay Adams, Parsippany, N.J.). The labeled fatty acid–albumin complex (12–20 $\mu$Ci in a volume of 2 ml of 0.15 M sodium chloride) was injected through the venous catheter in 10–15 sec. Blood samples of 2 ml were withdrawn at intervals from the carotid artery simultaneously with the withdrawal of each fetal blood sample. An equal volume of 0.15 M aqueous sodium chloride was injected into the venous catheter after each sample was obtained.

### Analyses

The liver, interscapular brown and perirenal white adipose tissues, and the cardiac ventricles of each fetus were rapidly weighed and homogenized in 20 vol of ethanol–acetone 1:1 (v/v). The decapitated carcass was homogenized separately. After incubation for 15 hr at 40°C, the homogenates were filtered and the filtrate was made to known volume. For estimation of triglycerides, portions of the filtrate were taken to dryness under nitrogen and the residue was dissolved in chloroform. Phospholipids were usually removed by batch treatment with silicic acid (200 mg/mg of lipid). In some experiments, cholesteryl esters, neutral glycerides, and phospholipids were separated on a column of silicic acid (6). Glyceride-glycerol (7) and lipid phosphorus (8) were estimated in appropriate fractions.

Lipids were extracted from 1 ml of plasma in 5 ml of Dole's mixture (9), and the extract was purified (10). The FFA were titrated in a two-phase system (9), and the FFA and neutral lipids were separated by a solvent-partition technique (11). The neutral lipid fraction was washed again with alkaline-ethanol solution in samples obtained during the first few minutes after injection of [1-$^{14}$C]palmitate to minimize contamination of the neutral lipids with traces of FFA of high specific activity. For assay of $^{14}$C, samples were evaporated to dryness in counting vials (1 $\mu$mole of palmitic acid was added as carrier to samples containing purified FFA). 10 ml of toluene containing 0.45% diphenyloxazole and 0.03% 1,4-bis-[2-(5-phenyloxazolyl)]-benzene was added, and $^{14}$C content was assayed in a liquid scintillation spectrometer to a precision of better than ±5%.

For determination of fatty acid composition, free fatty acids and neutral glycerides separated on columns of silicic acid were transesterified with 1% sulfuric acid in absolute methanol (12). The methyl esters were quantified by gas–liquid chromatography on a 1/8 inch × 11 ft column packed with 12% ethylene glycol succinate on firebrick at 186°C as described elsewhere (12). A sample of known composition was run with each batch, and fatty acid compositions were calculated by computer integration of the area under each curve.

Lipoprotein lipase was assayed in extracts of white and brown adipose tissue (13). Thin slices of the tissues were incubated in 5 vol of Krebs-Ringer bicarbonate buffer, pH 7.5, for 1 hr in the presence or absence of 32 $\mu$g of heparin/ml of medium. The mixture was then filtered, and 1 ml of the filtrate was added to a 10-ml Erlenmeyer flask containing 1.3 ml of incubation mixture at 37°C. The incubation mixture contained, at pH 8.3, 15 $\mu$moles of Tris–HCl, 75 $\mu$moles of NaCl, 20 mg of bovine serum albumin, and 500 $\mu$l of a mixture of 100 $\mu$l of 10% Intralipid and 400 $\mu$l of normal human serum that had been preincubated for 1 hr at 37°C. Samples of 0.5 ml were taken in duplicate immediately and after incubation for 60 min at 37°C, and the lipids were extracted into Dole's mixture. The fatty acids released were titrated in a single-phase system (14). Activity of lipoprotein lipase was taken as quantity of FFA produced (micromoles per gram tissue and hour) in the presence of heparin in the initial incubation mixture less that produced in its absence.

Content of cofactor protein for lipoprotein lipase from cow's milk was estimated as described previously (15) in whole serum, in VLDL, and in serum from which VLDL had been removed by ultracentrifugation.

## RESULTS

### Fatty acid composition of plasma and tissue lipids

FFA of fetal plasma were richer in linoleate than those of maternal plasma (**Table 1**), in agreement with observations of Hershfield and Nemeth (16). The composition of fetal FFA closely resembled that of lipids of fetal white and brown adipose tissues. Fatty acids of fetal hepatic and plasma triglycerides also had closely similar compositions; they differed from fetal FFA mainly in having less stearate and more linoleate. The dietary fatty acids of the dams contained substantially more palmitate and linoleate and less oleate than maternal FFA.

### Transport and metabolism of [1-$^{14}$C]palmitate

After intravenous injection of labeled palmitate into three dams at different times of gestation, $^{14}$C appeared rapidly in fetal lipids (**Table 2**). Within each litter the total amount of $^{14}$C recovered in a given fetus was independent of the time (from 3 to 125 min after injection) that it was removed from the uterus. 3 min after injection, the liver

TABLE 1. Fatty acid composition of maternal and fetal lipids

| Sample | Fatty Acids | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 12:0 | 14:0 | 14:1 | 16:0 | 16:1 | 18:0 | 18:1 | 18:2 | 18:3 | 20:4 | Unknown |
| | | | | | | *moles %* | | | | | |
| Maternal plasma FFA | | 1.8 | | 28.2 | 4.0 | 11.8 | 26.1 | 17.0 | 5.9 | | 3.6 |
| | | (0.9) | | (3.7) | (2.0) | (2.2) | (5.2) | (3.7) | (3.5) | | |
| Fetal plasma FFA | | 1.9 | | 25.5 | 4.0 | 10.5 | 23.8 | 23.6 | 8.5 | | 3.1 |
| | | (0.6) | | (0.8) | (0.9) | (1.8) | (6.0) | (3.6) | (4.5) | | |
| Fetal liver triglycerides | | 1.4 | | 21.7 | 1.8 | 5.6 | 24.8 | 30.8 | 12.1 | 1.3 | 1.2 |
| | | (0.3) | | (1.7) | (0.2) | (0.5) | (5.1) | (2.1) | (5.1) | | |
| Fetal plasma triglycerides | | 1.5 | | 23.9 | 2.5 | 6.5 | 24.1 | 29.3 | 10.4 | | 2.1 |
| | | (0.7) | | (3.5) | (0.6) | (1.4) | (5.3) | (4.3) | (5.8) | | |
| Fetal white adipose tissue | | 1.6 | | 26.8 | 2.5 | 11.8 | 26.3 | 21.4 | 8.8 | | 0.7 |
| | | (0.3) | | (4.6) | (0.5) | (1.5) | (5.1) | (2.8) | (4.2) | | |
| Fetal brown adipose tissue | | 1.9 | | 29.1 | 2.5 | 10.5 | 26.5 | 20.0 | 8.1 | | 1.0 |
| | | (0.5) | | (5.2) | (0.6) | (1.5) | (5.1) | (3.3) | (4.1) | | |
| Food pellets | 0.3 | 0.2 | 0.4 | 37.0 | 1.6 | 6.9 | 16.3 | 30.2 | 7.2 | | |

Results are means ±SD (in parentheses) for five pregnant animals (gestational age 52–68 days) and their fetuses.

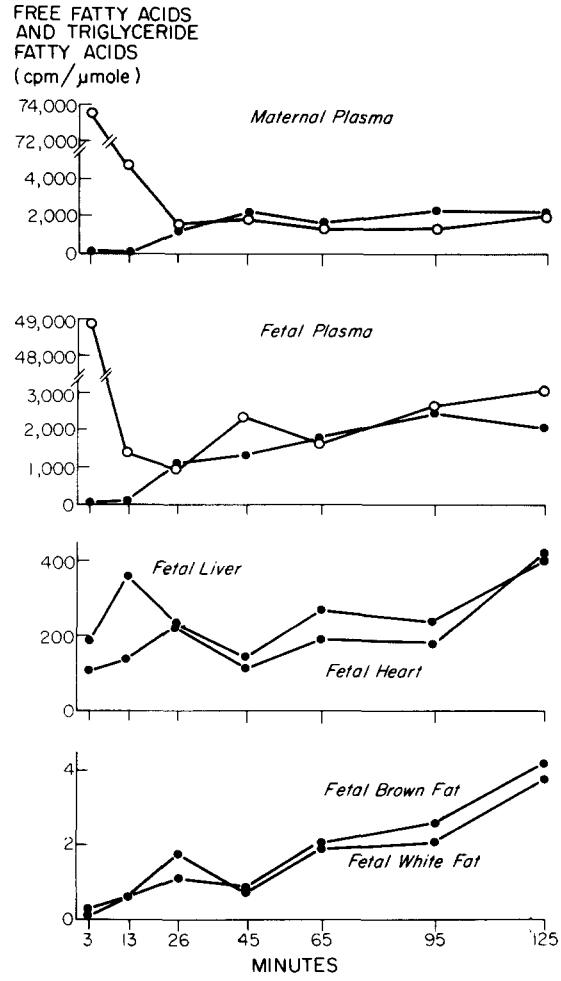


**Fig. 1.** Specific activity of FFA (○) and TGFA (●) in plasma and tissues after injection of [1-$^{14}$C]palmitate into a dam at 50 days of gestation.

contained 46–78% and after 13 min, 75–88% of the $^{14}$C in fetal lipids. The total percentages of injected $^{14}$C recovered in fetal lipids were 11, 16, and 20 in litters studied at 50, 62, and 70 days of gestation, respectively. No consistent time-dependent changes were observed in the amount of $^{14}$C in liver, heart, or carcass, but $^{14}$C accumulated progressively in fetal brown and white adipose tissue in all three experiments.

### Palmitate transport in the fetus

To evaluate the sequence of transport of palmitate more precisely, the time-dependence of specific activity of fatty acyl moieties of lipids in fetal tissues was calculated. After injection of labeled palmitate into dams, the specific activity of FFA fell rapidly in both dams and fetuses, and their absolute values were roughly comparable (**Fig. 1**). Very little radioactivity was present in fetal and maternal plasma triglycerides in samples obtained 3 and 13 min after injection; thereafter, it rose rapidly in both. The specific activity of fetal plasma FFA was generally of the same order as that

TABLE 2. Organ weights and distribution of injected radioactivity in the fetus after injection of [1-$^{14}$C] palmitate into dams

| Experiment no. | 1 | 2 | 3 |
|---|---|---|---|
| Fetal age (days) | 50 | 62 | 70 |
| Number of fetuses | 7[a] | 4[b] | 4[b] |
| Weight (g)[c] | | | |
| Liver | 1.7 (0.18) | 4.3 (0.7) | 4.0 (0.8) |
| Heart | 0.17 (0.024) | 0.33 (0.04) | 0.32 (0.05) |
| Brown and white adipose tissues | 0.61 (0.044) | 2.0 (0.3) | 3.3 (0.5) |
| Carcass | 32 (2.8) | 78 (0.5) | 83 (4.3) |
| Total fetus | 34 (3.0) | 81 (4.8) | 93 (4.8) |
| % of [1-$^{14}$C] palmitate injected into dam[c] | | | |
| Liver | 1.14 (0.82) | 3.17 (0.85) | 3.39 (1.80) |
| Heart | 0.094 (0.034) | 0.15 (0.00) | 0.064 (0.008) |
| Brown and white adipose tissues | 0.056 (0.039) | 0.26 (0.12) | 0.20 (0.12) |
| Carcass | 0.34 (0.12) | 0.49 (0.10) | 1.24 (0.15) |
| Total fetus | 1.53 (0.88) | 4.06 (0.93) | 4.89 (1.91) |

[a] One fetus at a time was removed 3, 13, 26, 45, 65, 95, and 125 min after injection.

[b] One fetus at a time was removed 3, 13, 26, and 45 min after injection.

[c] Mean values for fetuses in litter ± SD (in parentheses).

of plasma TGFA at times beyond 13 min and, in the youngest litter, it tended to increase after 26 min in both (Fig. 1). Specific activity of TGFA of white and brown adipose tissues consistently increased with time, but a significant amount was present before plasma TGFA were appreciably labeled, particularly in the two older litters. This pattern persisted when the specific activity of TGFA in adipose tissue of each fetus was expressed as a fraction of that of its hepatic TGFA (**Table 3**). Relative specific activity of myocardial TGFA increased after 13 min in the youngest litter but not in the older ones, and substantial amounts of $^{14}$C were invariably found in the heart at the two earliest time intervals. In a single experiment, specific activity of hepatic PLFA was found to be somewhat higher than that of TGFA. Specific activity of PLFA was too low to be measured in other tissues, and no $^{14}$C was detected in FFA in any tissue. In another experiment (not shown), fetuses were removed 2, 4, and 6 hr after injection of labeled palmitate. After 6 hr, specific activity of hepatic TGFA had fallen to 55% and that of myocardial TGFA to 67% of the 2-hr value, whereas that of plasma TGFA rose slightly and that of adipose tissue was unchanged.

### Factors related to fetal catabolism of plasma triglycerides

Because the progressive increase of $^{14}$C in TGFA of fetal adipose tissues after injection of [1-$^{14}$C]palmitate suggested that these TGFA were derived in part from plasma TGFA, we measured the activity of lipoprotein lipase in these tissues at two stages of gestation (**Table 4**). Activity of the enzyme in maternal adipose tissue fell late in gestation as described earlier in the rat (17), whereas that of fetal white and brown adipose tissues did not change appreciably. However, compared with values obtained by the same method in the fed adult rat (not shown), activity was low.

Blood plasma of adult guinea pigs contains very little high density lipoprotein and has almost no cofactor activity for lipoprotein lipase (15). Pooled serum from each of two litters of 55–70 days gestational age contained small but detectable amounts of cofactor activity. Addition of 0.03 ml

TABLE 3. Sequential changes of specific activities of fetal triglyceride fatty acids after injection of [1-$^{14}$C] palmitate into dams

| Fetal Age | Time after Injection | Liver | Other Organs | | |
|---|---|---|---|---|---|
| | | | Heart | White Adipose Tissue | Brown Adipose Tissue |
| *days* | *μ min* | *cpm/μmole* | *fraction of hepatic value* | *fraction of hepatic value X 1000* | *fraction of hepatic value X 1000* |
| 50 | 3 | 190 | 0.55 | 0.8 | 1.5 |
| | 13 | 360 | 0.40 | 1.7 | 1.8 |
| | 26 | 238 | 0.98 | 7.6 | 4.8 |
| | 45 | 144 | 0.80 | 5.0 | 6.0 |
| | 65 | 248 | 0.78 | 7.9 | 8.3 |
| | 95 | 240 | 0.75 | 8.9 | 10.6 |
| | 125 | 405 | 1.10 | 9.0 | 10.3 |
| 62 | 3 | 91 | 4.1 | 39 | 41 |
| | 13 | 82 | 6.6 | 87 | 91 |
| | 26 | 95 | 6.3 | 67 | 97 |
| | 45 | 105 | 5.5 | 93 | 74 |
| 70 | 3 | 39 | 6.3 | 13 | 15 |
| | 13 | 90 | 2.4 | 21 | 21 |
| | 26 | 115 | 1.8 | 22 | 26 |
| | 45 | 103 | 2.7 | 25 | 39 |

TABLE 4. Lipoprotein lipase activity in adipose tissue of fetuses and dams during early and late gestation

| | Age | Fetus | | Dam |
|---|---|---|---|---|
| | | White | Brown | White |
| | *days* | *μmoles/g × hr* | | *μmoles/g × hr* |
| "Early" | 55 | 1.7 | 3.5 | 15.6 |
| | 60 | 3.6 | 4.1 | 0.1 |
| | 64 | 1.4 | 3.1 | 4.5 |
| | 66 | 0.5 | 0.7 | 6.3 |
| | Mean | 1.8 | 3.2 | 6.5 |
| | SD | 1.3 | 1.6 | 5.5 |
| "Late" | 68 | | 2.0 | 0.5 |
| | 68 | 1.1 | 1.6 | 0.1 |
| | 70 | 5.7 | 3.7 | 0.2 |
| | 70 | 3.3 | 6.3 | 1.9 |
| | Mean | 3.3 | 3.4 | 0.6 |
| | SD | 2.3 | 2.0 | 0.9 |

of serum/mg of substrate triglyceride in a standard assay system containing lipoprotein lipase from cow's milk produced 51 and 26% of maximal enzyme activity; however, larger amounts of serum were inhibitory. Limited cofactor activity was detectable in VLDL from three litters as well as in serum from which VLDL had been removed by ultracentrifugation. By contrast, serum VLDL and VLDL-free serum from adult male and nonpregnant and pregnant female guinea pigs uniformly contained no more than trace amounts of cofactor activity.

## DISCUSSION

Polyunsaturated fatty acids accounted for 28–40% of the fatty acids in neutral lipids of fetal tissues. This indicates substantial transport of these compounds across the placenta of the guinea pig, as previously shown by Hershfield and Nemeth (16). Palmitate accounted for about one-fourth of the fatty acids of FFA and TGFA in plasma and of TGFA in tissues, suggesting that it is a suitable tracer for the metabolism of fetal fatty acids.

Most of the palmitate transferred across the placenta was rapidly deposited in hepatic lipids, mainly as TGFA. Taken together with the large content of polyunsaturated fatty acids in hepatic TGFA and the observation of Hershfield and Nemeth (16) that linoleic acid also readily tranverses the guinea pig placenta, this observation indicates that the fetal liver actively synthesizes triglycerides from exogenous fatty acids. During late gestation in the horse and pig, all of the blood, and, in other species, a major part of the blood from the umbilical vein passes through the hepatic sinusoids (18). Because uptake of FFA from the blood is a function of the distribution of blood flow (19), the fetal liver probably extracts immediately a large fraction of the FFA delivered from the placenta. As in other adult mammals (4, 6, 19–21), less than one-half of injected [1-$^{14}$C]palmitate is deposited in hepatic lipids of maternal guinea pigs (2).

We have calculated minimal values for unidirectional transport of FFA from dam to fetuses near term using the following data and assumptions: *1*, maternal plasma volume = 40 ml (5% of weight of dam less weight of combined fetuses); *2*, maternal plasma FFA = 0.5–0.6 μeq/ml (1) and half-life = 1 min (16); and *3*, 16–20% of FFA is transported across the placenta (amounts recovered in combined fetuses at 62 and 70 days of gestation). This gives a rate of transport of 14–16 μmoles of FFA/min in the dam with transfer of 2.2–3.2 μmoles/min to the combined fetuses. This amounts to 3.2–4.6 mmoles or about 0.9–1.3 g of FFA transferred per 24 hr. A guinea pig fetus increases its weight 6–8 g/day during late gestation (22) and has a fatty acid content of about 4% near term. For four fetuses in a litter, this gives a fatty acid accumulation of 1.0–1.3 g/day. Thus, placental transfer of FFA could account for the accumulation of lipid in the late gestational fetus. By a different approach, Hershfield and Nemeth reached a similar conclusion (16). Much of this FFA remains in the liver. In an average newborn guinea pig, the liver weighs 4 g, of which 1 g is triglycerides. This constitutes a substantial fraction of the stored fat that is used after birth in this species, which is less dependent on maternal milk for survival than most mammals.

The delay in appearance of $^{14}$C in both fetal and maternal plasma triglycerides after injection of labeled palmitate is comparable to that observed in other species (6, 11) and evidently represents the time required for synthesis and secretion of VLDL by the liver. Although the specific activities of fetal and maternal plasma TGFA were generally similar, placental transport of esterified fatty acids in the guinea pig, as in other mammals, is very limited (2, 3). The appearance of $^{14}$C in fetal plasma TGFA between 13 and 26 min after injection is therefore quite consistent with our earlier evidence (1) that the fetal guinea pig liver actively synthesizes and secretes very low density lipoproteins into the blood. The specific activity of fetal plasma TGFA subsequently exceeded that of the liver (Fig. 1). This result suggests the presence of at least two compartments of triglycerides in the fatty liver of the late gestational fetus. Presumably, one of these with low specific activity includes large fat droplets (6). The specific activity of hepatic TGFA did not fall during the first 2 hr after injection of labeled palmitate, consistent with the incorporation of a large fraction of the newly synthesized triglyceride into this particulate fat.

Because very little $^{14}$C appeared in plasma TGFA at short time intervals after injection of labeled palmitate, early deposition of $^{14}$C in lipids of fetal tissues most likely represents direct uptake and esterification of FFA from the blood. At later times, the specific activity of plasma FFA was generally comparable to that of plasma TGFA. This is

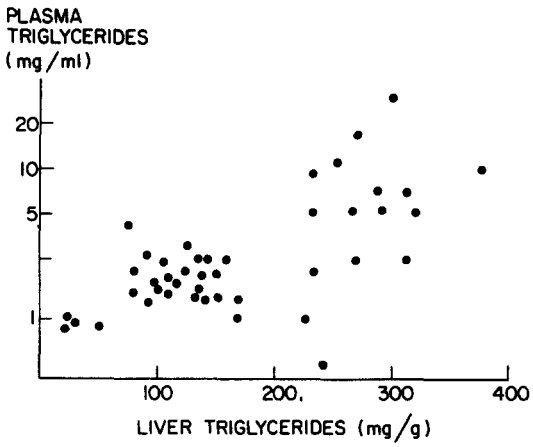


**Fig. 2.** Relationship between the concentration of triglycerides in fetal liver and plasma ($r = +0.57$). The values are taken from all animals in the present study and those reported previously (1). Gestational age ranged from 42 to 70 days.

consistent with derivation of at least some fetal FFA from hydrolysis of plasma TGFA, similar to that observed in adult animals (6, 21). The progressive accumulation of $^{14}C$ in adipose tissue lipids at these times therefore indicates that a substantial fraction of TGFA in this tissue may be derived from the liver via plasma TGFA. The lack of consistent increase of specific activity with time in myocardial TGFA suggests that palmitate was incorporated mainly from plasma FFA. Some of the deviations of the time-dependent changes of specific activity within litters shown in Table 3 presumably reflect variations in umbilical blood flow and in lipid content of organs and tissues.

Analysis of the combined data of the present study and our previous one (1) shows that triglycerides accumulate in both liver and plasma of the fetus near term. Further, as shown in **Fig. 2**, the concentrations of triglycerides in these tissues are positively correlated. If increasing content of triglycerides in liver were the result of inhibition of release of TGFA in VLDL, a negative correlation would be expected. The observed relationship suggests that the fatty liver and the hyperlipemia result from a common mechanism. Taken together with our morphological evidence of an active synthesis and secretion of VLDL in the fetal guinea pig (1), the present results, showing that about 80% of the large amount of FFA transferred to the fetus is initially removed by the liver, provide strong evidence that a high rate of hepatic synthesis of TGFA derived from FFA contributes to the hyperlipemia.

The capacity of extrahepatic tissues to metabolize VLDL triglycerides is more difficult to assess. Our data indicate that some of the TGFA accumulating in fetal adipose tissue is derived from plasma TGFA, but activity of lipoprotein lipase in this tissue was low. It is therefore quite possible that limitation of available enzyme in fetal adipose tissue contributes to the hyperlipemia.

Cofactor activity for lipoprotein lipase was higher in fetal than in adult guinea pigs. Because fetal blood plasma contains substantially more HDL than that of adults of this species (1), this observation is consistent with the postulated function of HDL as a reservoir for the cofactor protein (23). Cofactor activity in fetal plasma was, however, much lower than that observed in humans (15) and rats (24). The amount of this protein required at the surface of VLDL for optimal activity of lipoprotein lipase at its normal site of action in the capillary wall is not known, but the present in vitro observations raise the possibility that paucity of the cofactor protein may contribute to the hyperlipemia by limiting the activity of lipoprotein lipase on substrate triglycerides.

These studies were supported by U.S. Public Health Service grant HL-06285. Dr. Bøhmer was a U.S. Public Health Service International Postdoctoral Research Fellow (F05 TW 1490).

*Manuscript received 31 March 1975; accepted 23 July 1975.*

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