A Possible Defect in Triglyceride Transport in Idiopathic Hyperlipemia

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HYPERLIPEMIA is present in several pathologic and physiologic conditions such as idiopathic hyperlipemia, severe diabetes mellitus, nephrosis, certain liver and pancreatic diseases, von Gierke's disease, starvation, pregnancy, after ingestion of a fatty meal, etc. Remarks will be confined to idiopathic hyperlipemia.

It is well known that the increase in serum lipids in idiopathic hyperlipemia is due predominately to the triglyceride fraction although cholesterol and phospholipids are also elevated.[1–4] We have been interested in studying the metabolic defect which may be responsible for these changes. I should like to comment on the possible sites where the transport of triglycerides could be altered and present some of our preliminary findings with regard to a single specific defect.

POSSIBLE SITES OF ALTERATION

1. Intestinal Absorption. It can be seen in Fig. 1 that the intestinal absorption patterns after ingestion of 80 to 100 μc. of I^{131}-labeled triolein in normal subjects observed in our laboratory were comparable to those reported by Beres et al.[5] and Seller and associates.[6] However, the radioactivity of plasma total lipids measured at the same intervals after ingestion of I^{131}-labeled triolein were higher in idiopathic hyperlipemic patients than those observed in normal subjects (Fig. 2). Unfortunately it is difficult to determine if the elevated radioactivity of plasma lipids in idiopathic hyperlipemic patients is due to an increased rate in intestinal absorption or to a reduced rate of removal from the blood circulation. The disappearance curve following intravenous administration of I^{131}-triolein emulsion should provide information in differentiating these two possibilities.

2. Modification of Absorbed Fat in Intestinal Mucosal Cells. It is known that resynthesis of triglyceride may take place in intestinal mucosal cells.[7,8] Recent evidence has also suggested that some proteins attached to chylomicrons originate in the intestinal mucosa.[9] It is not likely that the ability of intestinal mucosal cells to resynthesize triglyceride is impaired, since our preliminary findings indicated that the appearance of the orally ingested I^{131}-labeled triolein in the plasma is mainly in triglyceride form.[10] However, information is not available with regard to the nature of proteins, cholesterol esters and phospholipids which are linked with chylomicrons in idiopathic hyperlipemia.

3. Modification of Chylomicrons in Intravascular Compartment. Rodbell and associates[9] have shown that the plasma does not contribute to the major portion of the A protein, one of the three proteins associated with chylomicrons. However, further linkage of chylomicrons with other protein(s), may take place in the intravascular compartment. Meng et al.[11] have shown that the mobility of triglyceride emulsion particles measured after incubation with serum or serum globulins was considerably reduced. Histidine, nucleoproteins or protamine exhibit more profound effects

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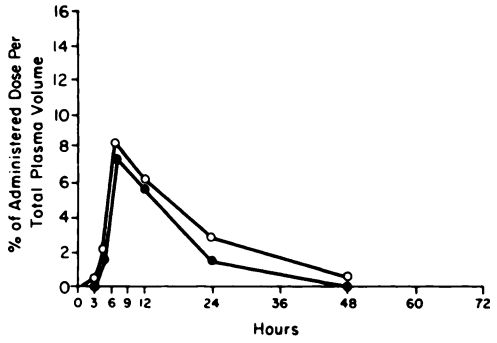

FIG. 1. Fat tolerance curve obtained after oral administration of 100 μc. of I^{131}-labeled triolein in a normal adult male subject showing the radioactivity of plasma total lipids and its rate of disappearance from the blood circulation. ○——○ = whole plasma; ●——● = plasma lipids.

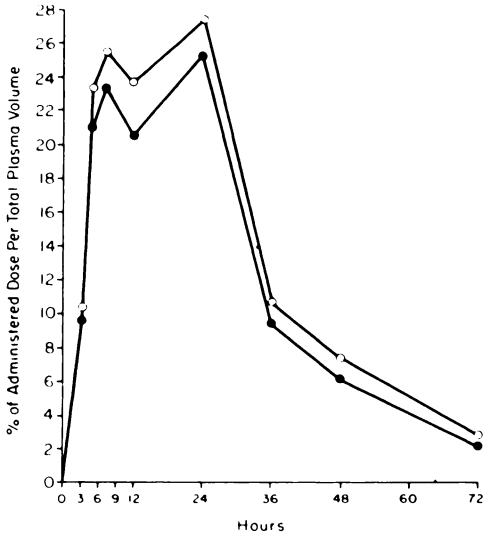

FIG. 2. Fat tolerance curve obtained after oral administration of 50 μc. of I^{131}-labeled triolein in a seven year old girl with idiopathic hyperlipemia showing the elevated radioactivity of plasma total lipids and the reduced rate of its removal from the blood circulation. ○---○ = whole plasma; ●——● = plasma lipids.

on chylomicron mobility. Thus, it is possible that in idiopathic hyperlipemia the nature and composition of these proteins associated with chylomicrons may be altered in the intestinal mucosal cells, in the lacteals or in the blood stream which render the transport of chylomicrons difficult resulting in accumulation in the intravascular compartment. Again, studies of the disappearance of intravenously

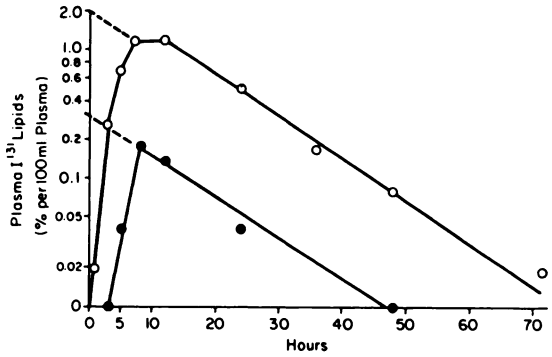

FIG. 3. Showing the disappearance curve of I^{131}-labeled plasma lipids in a normal and an idiopathic hyperlipemic subject. The half-life in the normal subject is seventeen hours and that of the idiopathic hyperlipemic patient is twenty-four hours. ●——● = normal subject (E. S.); ○——○ = idiopathic hyperlipemic subjects (F. M.).

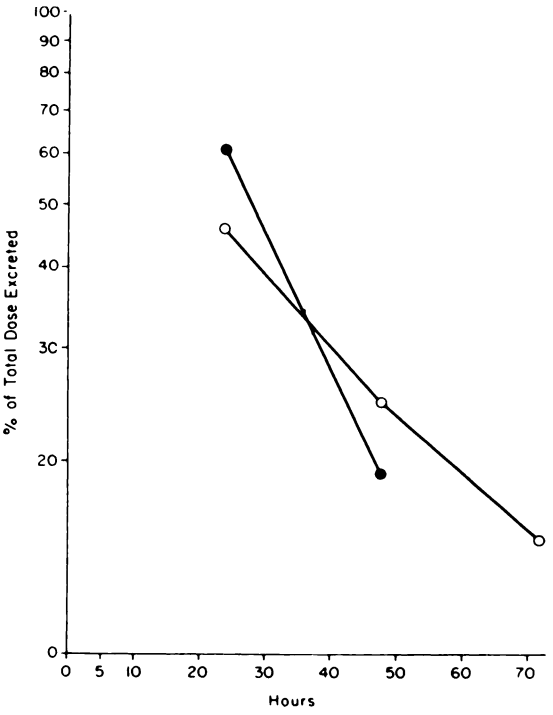

FIG. 4. Showing the delayed urinary excretion of inorganic I^{131} following oral administration of I^{131}-labeled triolein in an idiopathic hyperlipemic subject. ●——● = normal subject (J. B.); ○——○ = idiopathic hyperlipemic subject (B. F.).

administered I^{131}-triolein emulsion might rule out any contribution of the intestinal mucosal cells or passage in the lacteals to the elevation of plasma lipids.

TABLE I
Effect of Heparin on Plasma Lipids

Patient	Time of Blood Withdrawal (Relative to Heparin)	Plasma Lipids			
		Free Fatty Acids (mEq./L.)	Total Fatty Acids (mg. %)	Total Cholesterol (mg. %)	Lipid Phosphorus (mg. %)
B. E.	Before heparin	...	2,030	293	13.5
	30 min. after	...	1,900	286	12.5
F. M.	Before	0.62	2,165	304	18.7
	30 min. after	2.52	2,015	274	15.0
H.	Before	1.04	914	393	11.9
	3 min. after	2.09	918	375	12.5

TABLE II
Effect of Heparin on Plasma Lipoproteins

Patient	Time of Blood Withdrawal (Relative to Heparin)	Plasma Lipoproteins*			
		Prealbumin (%)	Albumin-Alpha (%)	Beta (%)	Total Area
B. E.	Before heparin	0	11.4	88.6	136.5
	30 min. after	0	31.1	68.9	103.0
F. M.	Before	0	5.0	95.0	70.7
	30 min. after	2.9	25.6	71.5	62.8
H.	Before	0	15.6	84.4	51.5
	3 min. after	2.7	33.3	64.0	45.0

* Determined by paper electrophoretic technics.

4. Removal of Chylomicrons from Intravascular Compartment. The accumulation of triglycerides in the intravascular compartment in idiopathic hyperlipemic patients may arise from two causes: (1) decreased rate of removal from the blood stream to other tissues and (2) increased synthesis and accelerated mobilization from tissues to the blood circulation. Results of our studies seem to favor retarded removal.

Thannhauser and Stanley[1] first found that the radioactivity of serum total lipids, measured at intervals after oral ingestion of I^{131}-labeled olive oil, was much higher and the rate of disappearance from the blood stream was considerably slower in idiopathic hyperlipemic patients than in normal persons. Furthermore, the urinary excretion of inorganic I^{131} was lower in idiopathic hyperlipemic patients than in normal subjects. It is readily seen in Figures 3 and 4 that we have confirmed these findings. The uptake of inorganic I^{131} by the thyroid was blocked by the administration of Lugol's solution for two to three days prior to the test in all patients.

The elevation of plasma triglycerides in hyperlipemic patients was apparently not entirely due to the presence of a large triglyceride pool. Crofford and associates[12] demonstrated that the I^{131}-labeled triolein tolerance curve remained high even when the patient was non-hyperlipemic when maintained on a diet furnishing only 1,200 calories per day.

The accumulation of triglycerides in the blood stream is probably not due to the inability of tissue cells to utilize or oxidize the fatty acids. When I^{131}-labeled oleic acid was injected intravenously in the form of an oleic acid-serum albumin complex, the radioactivity disappeared from the blood circulation at the same rapid rate in idiopathic hyperlipemic patients as in normal subjects, with an immediate increase in urinary excretion of inorganic I^{131}.[12]

These results suggest that tissue cells are capable of utilizing the I^{131}-labeled fatty acid when it is made available to them. Studies are in progress to substantiate these observations.

The mechanism of this defect which delays the removal of triglycerides from the blood stream in idiopathic hyperlipemia is not clear. It may be pointed out that the response to intravenous administration of heparin was at least qualitatively normal. It can be seen in Tables I and II that (1) the usual increase in plasma free fatty acids was observed; (2) the expected decrease in plasma total fatty acids occurred in most instances although the changes were not very great; (3) changes in lipoprotein patterns measured by paper electrophoretic technics showed a decrease in total staining area, a decrease in beta-lipoproteins, an increase in albumin-alpha lipoproteins and the appearance of a prealbumin fraction. Other investigators have found similar results in normal and hyperlipemic patients.[13-15] However, it is conceivable that the delayed removal of triglycerides from the intravascular compartment may be due to a lack of "endogenous" lipemia clearing factor or/and increase in clearing factor inhibitor. Hollett and Meng[16] and others[17,18] have found a lipemia-clearing inhibitor in plasma of normal human subjects and animals. Klein and Lever[19] have demonstrated an increase in clearing inhibition by the serum of idiopathic hyperlipemic patients.

6. Transport of Triglyceride Across the Cell Membrane. Information is not available concerning the transport of glycerides across the cell membrane in normal or pathologic conditions. It is possible that the uptake of chylomicrons by the cells is impaired in idiopathic hyperlipemic patients. It may also be possible that the synthesis of triglyceride by the tissues is increased or the fat mobilization from the depots is accelerated. Undoubtedly much work remains to be done to unfold the mechanism of elevation of blood triglycerides in idiopathic hyperlipemia.

SUMMARY

The radioactivity of plasma total lipids determined at intervals after oral ingestion of I^{131}-labeled triolein were much higher in idiopathic hyperlipemic patients than in normal individuals. The excretion of inorganic I^{131} in the urine in hyperlipemic patients was slower. The experimental evidence obtained in our laboratory and by other investigators, particularly that of Crofford et al.,[12] suggests that this might be due to a decrease in the removal of triglycerides from the circulation.

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