

Table 5. Turnover rate, splanchnic mobilization and uptake of plasma FFA in  $\mu\text{mol per minute and m}^2$  body surface area

Subject	Turnover rate	Splanchnic mobilization		Splanchnic uptake	
		mini- mum value	maxi- mum value	mini- mum value	maxi- mum value
R.E.	306±15	89±19	140±33	194±12	245±16
P.L.	308±41	5±26	15±33	126±42	137±50
E.S.	262±6	56±12	84±14	117±8	144±7
R.M.	102±5	45±6	71±11	91±0	117±5
F.G.	445±24	105±36	190±74	268±74	352±56
R.S.	242±16	41±7	66±13	121±11	147±13
K.H.	372±26	89±11	157±11	176±23	244±22
G.B.	411±11	239±47	360±85	388±41	510±69
P.N.	234	71	137	188	255
L.N.	329±21	65±32	87±47	127±31	150±45
R.M.	233±15	52±7	85±15	92±10	126±16
G.J.	241±17	30±4	45±7	103±13	118±16
N.H.	235±12	50±6	73±5	70±8	92±11
B.P.	314±53	92±42	166±83	218±71	291±110
B.L.	321±14	130±32	265±112	223±19	358±99
O.S.	225±6	39±4	84±10	115±9	160±14
I.E.	464±27	88±6	112±9	219±12	243±3
B.A.	278±17	53±18	93±33	126±26	161±41
L.E.	200±9	35±13	53±22	82±12	100±20
K.L.	361±33	118±58	220±125	201±51	304±119
H.M.	203±35	67±10	101±19	81±9	116±0
K.M.	275±10	39±8	61±14	169±12	191±16
E.J.	273±10	102±16	165±24	209±12	272±12
H.G.	364±20	37±15	55±25	128±20	146±29
L.J.	289±10	87±7	122±9	156±13	191±15
B.H.	215±9	31±7	49±11	85±5	103±9
E.H.	201±5	46±7	83±16	96±3	133±11
Y.I.	210±16	63±3	85±9	127±3	149±7
N.L.	356±17	103±6	183±23	190±2	269±19
K.O.	227±25	63±10	108±16	130±9	169±11
H.N.	192±0	79±1	159±3	111±4	191±5
A.A.	202±8	51	84	84	118
R.H.	184±11	13±7	17±10	77±9	81±9
N.J.	192±6	50±8	87±19	143±9	180±19
A.H.	156±6	51±7	82±15	131±10	162±12
K.K.	196±17	80±38	111±52	131±27	162±41
E.N.	310±9	51±2	88±5	140±8	178±10
G.H.	261±5	105±23	166±38	168±9	228±19
J.P.	249±7	60±12	103±19	123±4	166±7
T.J.	439±10	59±21	109±45	157±34	209±56
N.N.	296±6	106±10	169±18	178±3	238±9
H.H.	307±14	40±4	61±7	83±10	108±13

Mean value and standard error of the mean for determinations made at 180, 210 and 240 min in each subject.

bilization ( $r=0.27$ ,  $p>0.05$ ) or for maximum FFA uptake ( $r=0.35$ ,  $p>0.05$ ).

#### Relationship between Chemical TG Secretion Rate and Plasma FFA Transport.

The chemical secretion of plasma TG was positively correlated to all three plasma FFA transport parameters (Fig. 6 and Table 7). As there was a high degree of intercorrelation between the FFA transport parameters partial correlation analysis was made (Table 7). This shows in essence that the relationship between chemical TG secretion rate and FFA transport is due to the effect of FFA uptake in the splanchnic region. The linear regression lines

Table 6. Turnover rate, maximum splanchnic mobilization and uptake of plasma FFA in  $\mu\text{mol per minute and m}^2$  body surface area in normotriglyceridaemic and hypertriglyceridaemic subjects. Mean values  $\pm$  SEM are given

	Turnover rate	Maximum splanchnic	
		mobilization	uptake
Normotriglyceridaemia ( $n=28$ )	289±15	121±14	206±18
Hypertriglyceridaemia ( $n=14$ )	243±19	98±11	161±12

Table 7. Correlation and partial correlation coefficients for relationship between values for the three methods for plasma TG "turnover rate" (y) and plasma FFA turnover rate and splanchnic FFA mobilization and uptake in subjects with normal plasma TG concentration

(x)	Plasma TG "turnover rate" (y)		
	Chemical secretion method	Clearance method	Isotope secretion method
FFA turnover rate	0.52**	0.55**	0.65***
eliminating the effect of splanchnic FFA mobilization	0.26 <sup>ns</sup>	0.43*	0.51**
splanchnic FFA uptake	0.17 <sup>ns</sup>	0.38*	0.51**
Splanchnic FFA mobilization	0.58**	0.45*	0.65***
eliminating the effect of splanchnic turnover rate	0.45*	0.07 <sup>ns</sup>	0.51**
splanchnic FFA uptake	-0.12 <sup>ns</sup>	0.07 <sup>ns</sup>	-0.12 <sup>ns</sup>
Splanchnic FFA uptake	0.66***	0.46*	0.73***
eliminating the effect of FFA turnover rate	0.58**	0.17 <sup>ns</sup>	0.54**
splanchnic FFA mobilization	0.40*	0.13 <sup>ns</sup>	0.44**

\* $p<0.05$ , \*\* $p<0.01$ , \*\*\* $p<0.001$  and <sup>ns</sup>=not significant = $p>0.05$

and the intervals of 99 per cent confidence for the normo-triglyceridaemic subjects are shown in Fig. 6. Most of the patients with hypertriglyceridaemia fall inside the zones of 99 per cent confidence. Five patients (H.H., K.K., J.P., T.J. and G.H.), however, fall outside this zone with relatively higher TG secretion rates for given "FFA transport rate" values.

#### Relationship between Plasma TG Clearance Rate and Plasma FFA Transport.

The plasma TG clearance rate was positively correlated to the three FFA transport parameters (Fig. 7 and Table 7). However since the intercorrelations between the three FFA transport parameters were significant the data on the normo-triglyceridaemic subjects were subjected to partial correlation (Table 7). Regression analysis of the same data was also made and is presented in Fig. 7. Three patients with hypertriglyceridaemia fall within the limits of 99 per cent confidence for the relationship between plasma TG clearance and FFA turnover rate and five

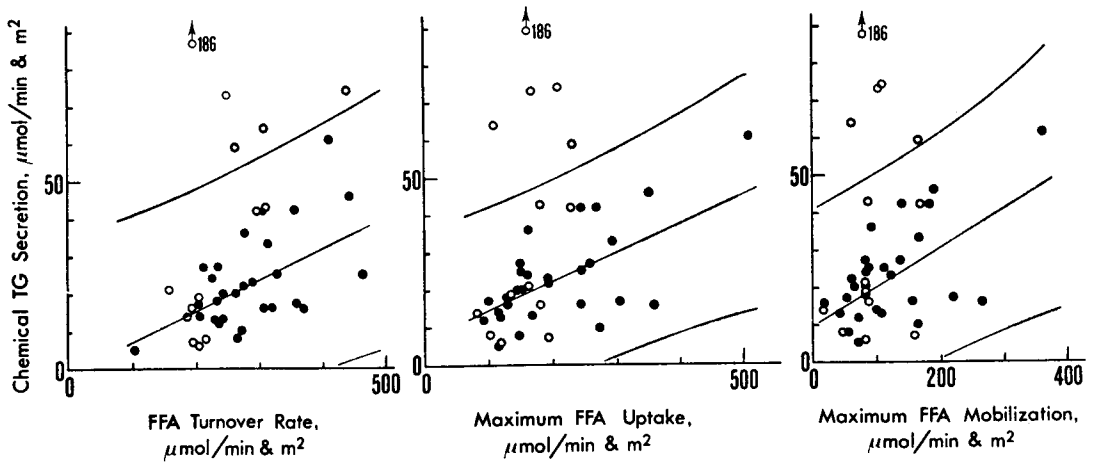


Fig. 6. Relationship between splanchnic chemical plasma TG secretion and total and splanchnic plasma FFA transport in normotriglyceridaemic (closed circles) and hypertriglyceridaemic (open circles) subjects. Regression line and zones for 99 percent confidence are indicated

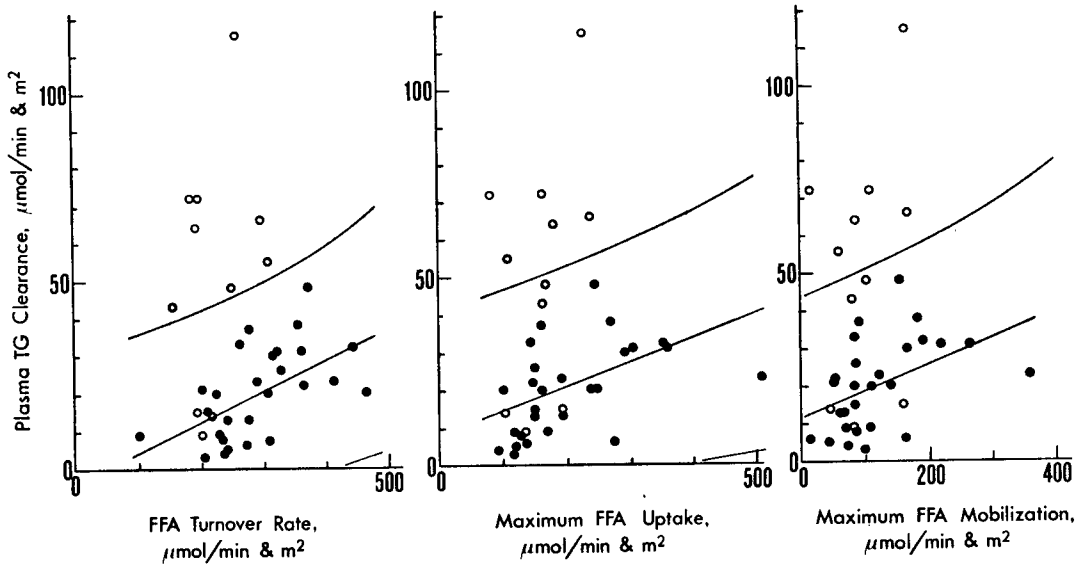


Fig. 7. Relationship between plasma TG clearance and total and splanchnic plasma FFA transport in normotriglyceridaemic (closed circles) and hypertriglyceridaemic (open circles) subjects. Regression line and zone of 99 per cent confidence are indicated

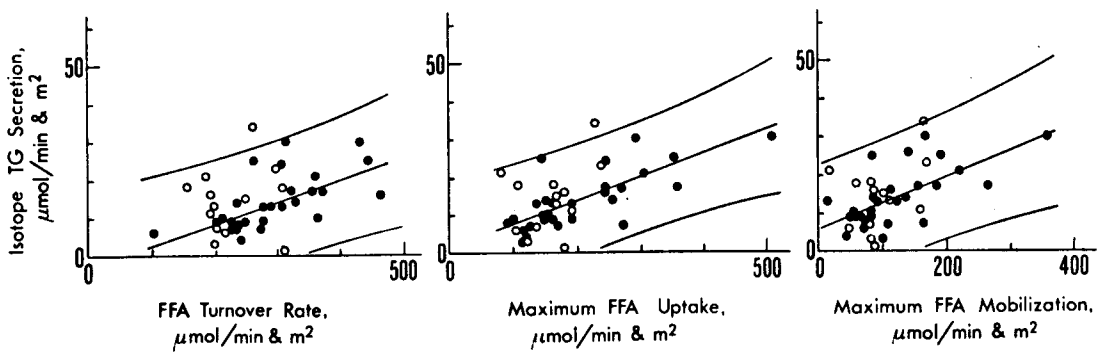


Fig. 8. Relationship between splanchnic isotope plasma TG secretion and total and splanchnic plasma FFA transport in normotriglyceridaemic (closed circles) and hypertriglyceridaemic (open circles) subjects. Regression line and zone of 99 per cent confidence are indicated

patients fall within the same limits for the relationships between plasma TG clearance and splanchnic FFA uptake and mobilization.

#### *Relationship between Isotope TG Secretion Rate and Plasma FFA Transport.*

Significantly positive correlations were found between isotope TG secretion and the parameters for total and splanchnic turnover of plasma FFA among normo-triglyceridaemics (Fig. 8 and Table 7). However, partial correlation analysis (Table 7) showed that the correlation between splanchnic TG secretion and FFA mobilization disappeared when the effect of splanchnic FFA uptake was eliminated. Regression lines and limits for 99 per cent confidence are shown in Fig. 8. Only one patient with hypertriglyceridaemia (G. H) fell outside the 99 per cent confidence interval.

### Discussion

In the present study plasma TG "turnover rate" has been estimated by three different methods which have been described previously [6, 11, 12], the splanchnic chemical TG secretion method, the plasma TG clearance method and the splanchnic isotope TG secretion method. The three methods are mathematically independent of each other and the assumptions on which they are based differ.

#### *The Chemical TG Secretion Method*

This method is the most direct and measures the net splanchnic secretion of plasma TG (or to be correct glyceride-glycerol). It makes no assumptions about the nature of the precursor for the triglyceride fatty acids (TGFA), which could be fatty acids taken up from plasma, fatty acids derived from lipogenesis in the splanchnic region or fatty acids made available from liver TG pools.

This method does not permit correction for any TG uptake in the splanchnic region or estimation of any inflow of TG into plasma from extra-splanchnic tissues. Both these mechanisms, if operating in the fasting state, would lead to an underestimate of plasma TG "turnover rate".

#### *The Plasma TG Clearance Method*

This method is based on two assumptions. First, that all secretion of labelled TG into the circulation takes place in the splanchnic area. Secondly, that the plasma TG removed from the blood have VLDL-TG specific radio-activity. Since results obtained with this method and the chemical secretion method are similar, the latter assumption would seem to be valid. Havel *et al.* [27] and others [28-30] have also shown these assumptions to be valid.

#### *The Isotope TG Secretion Method*

This method depends on several assumptions. The most important is that all liver fatty acids used for

VLDL-TG syntheses must be in complete equilibrium with or have a specific radio-activity identical to hepatic vein FFA. If all fatty acids for VLDL-TG synthesis were derived from plasma FFA and if palmitic acid is a representative tracer for FFA the method would be valid. However, splanchnic secretion rates obtained with this method are lower than those obtained with the chemical method. Despite this, the two methods were significantly correlated for values below 40  $\mu\text{mol}/\text{min. and m}^2$  but not for higher values. It is possible that this method only measures that part of splanchnic plasma TG secretion which is derived from plasma FFA. This would be consistent with the close correlation found between isotope TG secretion and the transport parameters for plasma FFA for the whole material (Fig. 8).

In the case of the two other methods for plasma TG "turnover rate" and in contrast to the isotope TG secretion method, several hypertriglyceridaemic patients fell outside the zones of 99 per cent confidence for the relationship between TG "turnover rate" and the FFA transport parameters (Figs. 6 and 7).

This method may thus underestimate plasma TG turnover rate and the underestimation may, perhaps, be more pronounced in the case of hypertriglyceridaemia. However, comparison with the other two methods may give a better understanding of the pathogenesis of hypertriglyceridaemia (see below), especially with regard to the precursor of plasma TGFA.

#### *Relationship between Plasma TG Levels and TG "Turnover Rates"*

Transport often follows first order kinetics in biological systems [31]. This means that the transport rate is directly proportional to the concentration. Assuming first order kinetics the transport of VLDL-TG could be formulated as follows:

$$\text{TG-TOR} = K \times \text{VLDL-TG} \times \text{PV}$$

where TG-TOR = turnover rate of plasma TG,  $\mu\text{mol}/\text{min.}$

K = fractional turnover rate of plasma TG, per min.

VLDL-TG = concentration of plasma VLDL-TG,  $\mu\text{mol}/\text{l}$

PV = plasma volume, l.

From this it follows that

$$\text{VLDL-TG} = \frac{\text{TG-TOR}}{K} \times \frac{1}{\text{PV}}$$

Plasma volume variations would be unlikely to lead to more than minor alterations in VLDL-TG. Furthermore, TOR values have been expressed per  $\text{m}^2$  body surface to compensate for such variations. Thus the two major factors left to influence the level of TG are its turnover rate and the fractional turnover rate. For example when the VLDL-TG level increases in hypertriglyceridaemia from 1 to 10  $\text{mmol}/\text{l}$  either the turn-

over rate must have increased 10 times or the fractional turnover rate must have decreased 10 times unless both mechanisms have induced the hypertriglyceridaemia together.

To what extent do our two methods which give the highest values for plasma TG transport measure plasma VLDL-TG turnover rate? Although available evidence suggests that the liver is the major source of the endogenous plasma TG, it is unlikely that splanchnic secretion rate is identical with the turnover rate of plasma TG. Most probably an uptake of plasma TG occurs in splanchnic viscera. This would cause the values for net splanchnic TG secretion rates, measured with the present technique, to be lower than plasma TG turnover rate. Assays of blood samples taken from the portal vein are necessary to solve this problem. It is also possible that in man fasted for 12–16 h TG are secreted into the circulation at places other than the splanchnic region. Studies in men who have fasted 12 to 16 h have shown that the lymph secretion rate from the thoracic duct into the blood circulation is about 1 ml/min. [32]. The TG concentration of this lymph may vary depending on the fat content of the last meal. However, on average, it is reasonable to estimate that in the present studies about 1  $\mu\text{mol}$  TG per minute and  $\text{m}^2$  body surface area entered the blood as lymph TG: a figure which in most subjects is rather small compared to the values for TG "turnover rate". It has also been estimated in the rat under certain conditions that about 10 per cent of total VLDL-TG may arise from thoracic duct lymph [3].

These findings suggest that our estimates of plasma TG turnover by the chemical TG secretion method and the plasma TG clearance method do not seriously underestimate plasma TG turnover rates. We will, therefore, refer to our estimates with these methods as "turnover rates" in spite of the limitations discussed above.

The average plasma TG "turnover rate" was 20  $\mu\text{mol}/\text{min. and m}^2$  body surface area in subjects with normal plasma TG concentrations. This corresponds to 60  $\mu\text{mol}/\text{min. and m}^2$  of TGFA (unless mono- and diglycerides were the major components of glyceride-glycerol). Recently two reports on plasma TG turnover, estimated with apparently reliable methods, have appeared [27, 28]. Mean values of plasma TG turnover rate presented for normotriglyceridaemics were 23 and 58  $\mu\text{mol TGFA per minute and m}^2$ . In both these reports only a few subjects were studied. Earlier methods [33, 34] have been shown to underestimate plasma TG turnover rate considerably [6, 12, 35].

The splanchnic FFA uptake was on the average about 200  $\mu\text{mol}/\text{min. and m}^2$  body surface area. This would provide enough fatty acids for plasma TG synthesis even taking into account the fact that ketone body production requires about 40  $\mu\text{moles}$  of fatty acids per minute and  $\text{m}^2$  [27, 36].

From the point of view of caloric homeostasis the respective plasma FFA and TGFA transport of about

300 and 60  $\mu\text{mol}/\text{min. and m}^2$  body surface area require about 7400 and 1500 moles  $\text{O}_2$  for complete oxidation. This corresponds to 123 and 25 per cent respectively of basal  $\text{O}_2$  consumption (6000  $\mu\text{mol}/\text{min. and m}^2$  in normal men about 50 years of age). In this connection, it is of interest that myocardial uptake of plasma TG in resting, fasting healthy men may provide 10 to 20 percent of the heart's energy supply [37].

#### *Mechanisms of Hypertriglyceridaemia*

As discussed above the plasma TG level is mainly regulated by the turnover rate and the fractional turnover rate.

The plasma TG "turnover rates" for the normo- and hypertriglyceridaemic subjects were essentially in the same range except for one hypertriglyceridaemic patient, whose "turnover rate" was increased about twofold above "normal". The "fractional turnover rate", however, was in general lower in hyper- than in normotriglyceridaemic subjects. This suggests a removal defect in hypertriglyceridaemia measured as reduced fractional removal rate. The inflow of TG into plasma is also of importance for setting plasma TG levels. Subjects with plasma TG "turnover rates" in the upper part of the range may be more likely to get hypertriglyceridaemia if removal capacity is impaired than if fractional removal rate is high. This is illustrated in Fig. 3, where there are good correlations between VLDL-TG concentrations and the TG "turnover rates" for hyper- but not for normotriglyceridaemic subjects. This might explain in part the data of Reaven *et al.* [34] who concluded that hypertriglyceridaemia is caused by increased plasma TG "turnover rate". In addition, however, there are criticisms of their method for plasma TG turnover determination [35].

A defect in removal of plasma TG in patients with hypertriglyceridaemia has been suggested in several reports [27–30, 33, 38]. A removal defect has also been found in the case of exogenous TG where a hyperbolic relationship existed between plasma TG concentration and fractional removal rate [39]. Further studies are needed to elucidate the underlying mechanism of this defect in removal of TG from plasma. However, in patients with hypertriglyceridaemia, decreased lipoprotein lipase activities have been demonstrated in human adipose tissue [40] and also in plasma after heparin administration [41].

#### *The Importance of Total and Splanchnic Turnover of Plasma FFA in Determining Plasma TG "Turnover Rates"*

The hypothesis that flux of plasma FFA to the liver might be a determining factor for plasma TG production was discussed in detail earlier [1]. Several studies available at that time favoured this hypothesis. Labelled FFA injected intravenously soon appeared in plasma TG in rats [42, 43] in rabbits [44] in dogs

[45] and in man [46, 47]. Hepatectomy abolished this incorporation in rats [43] and dogs [45]. Furthermore, in man after intravenous injection of labelled palmitate, plasma TG radio-activity in hepatic vein blood was demonstrated to be higher than the TG radio-activity in arterial blood [48]. Also *in vitro* perfusions of rat [49, 50] and dog [51] livers showed that the secretion rate of TG into the perfusate was related to the hepatic uptake of FFA. In the present study the results very strongly support this hypothesis in subjects with plasma TG within the normal range (Table 7) and in some patients with hypertriglyceridaemia (Figs. 6–8). Significant positive correlations were obtained between plasma TG "turnover rates" and all three plasma FFA transport parameters (Table 7). However, when these correlations were subjected to partial correlation analysis the relationship between plasma TG "turnover rate", measured by either of the three methods, and splanchnic FFA mobilization disappeared when splanchnic uptake was kept constant. This indicates that in subjects with normal plasma TG concentrations the plasma TG "turnover rates" depend very much on splanchnic FFA uptake. This has also been demonstrated by Havel *et al.* [27]. In the case of hypertriglyceridaemics, some patients fell inside this relationship while others did not. The patients who fell significantly outside the relationship between splanchnic chemical TG secretion and splanchnic FFA uptake may constitute a separate population. They have high splanchnic plasma TG secretion rates in relation to FFA turnover rate and the TG secreted may thus have precursors other than plasma FFA for their synthesis in the liver. Such precursors may be carbohydrates or liver TG derived from other sources. The five patients, who fell outside the relationship between splanchnic chemical TG secretion and plasma FFA turnover rate included one with xanthoma tuberosum and type III and four with type IV lipoprotein patterns. Of those with type IV pattern, two had sinking pre-beta-lipoprotein and one had a high cholesterol/TG ratio in the VLDL which, however, migrated as pre-beta-lipoprotein on paper electrophoresis.

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