Uptake of Individual Free Fatty Acids by Skeletal Muscle and Liver in Man

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ABSTRACT Arterial-venous concentration differences for individual free fatty acids (FFA) were measured across the deep tissues of the forearm, the splanchnic vascular bed, and the kidney in healthy, postabsorptive subjects. In addition, arterial-portal venous FFA differences were determined in five patients undergoing elective cholecystectomy.

The differences in fractional uptake among the individual FFA across the forearm were small and not statistically significant. Splanchnic fractional uptake was high for FFA with short chain lengths and rose with increasing degree of unsaturation. Small, negative arterial-portal venous differences for individual FFA were observed, indicating that arterial-hepatic venous FFA differences mainly reflect hepatic uptake. When the arterial FFA concentration was reduced to approximately 25% of the control values by the administration of nicotinic acid, net uptake of total FFA ceased but there was release of stearic acid and uptake of lauric, myristic, and palmitoleic acid to the splanchnic region. Muscle and liver uptakes of individual FFA were both dependent on their arterial concentrations with the exception of the splanchnic uptake of stearic acid. There was no uptake of free arachidonic acid by either muscle or liver, nor was there significant uptake of any of the free fatty acids by the kidney. It is concluded (*a*) that there are important quantitative differences between the net exchanges of individual FFA across the splanchnic vascular bed, (*b*) that tracer studies of FFA metabolism require the determination of individual FFA specific activities, (*c*) that palmitic and oleic acid appear to be suitable tracers for the entire FFA fraction in most instances.

INTRODUCTION

The free fatty acid (FFA)[1] fraction in plasma is made up of both saturated and unsaturated fatty acids of varying chain lengths and the concentration of each acid is determined by the balance between its release from adipose tissue and its uptake in various FFA-utilizing organs. Studies both in vitro and in vivo have indicated that the fatty acids differ in their rate of release from adipose tissue, the rate rising with decreasing chain length and increasing unsaturation (1, 2). Their uptake in several tissues in man has likewise been found to differ (2–6). Such differences in individual FFA turnover are of interest not only with regard to the mechanisms involved in uptake and metabolism, but also in view of the widespread use of a single labeled FFA as a tracer for the entire plasma FFA fraction in studies of regional or whole-body FFA metabolism.

The present study was undertaken to characterize further the net uptake of individual FFA by skeletal muscle and liver, the two major sites of FFA removal in the postabsorptive state. The concentrations of individual FFA were determined by gas chromatography in repeated samples from a deep forearm vein, draining almost exclusively muscle, a hepatic vein, and an artery. In addition, arterial and portal venous concentration differences for FFA were examined in subjects undergoing elective cholecystectomy, to evaluate the influence of splanchnic extrahepatic tissues on net splanchnic FFA uptake. The splanchnic uptake of FFA was further studied at low arterial concentrations induced by the administration of nicotinic acid. Finally, the FFA exchange across the kidney was examined in one subject.

METHODS

Subjects. Healthy male volunteers (mean age 29 yr, range 21–57 yr) ingesting a mixed diet were studied in the overnight fasted state. In addition, five patients (four female and one male, age 32–50 yr) undergoing elective cholecystectomy were studied during the surgical procedure. No special dietary regimen was applied.

Procedure. Teflon catheters were inserted percutaneously into a deep forearm vein in the retrograde direction

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[1] *Abbreviations used in this paper:* A-DV, arterial-deep venous; A-HV, arterial-hepatic venous; A-RV, arterial-renal venous; ESBF, estimated splanchnic blood flow; FFA, free fatty acid; NA, nicotinic acid.

TABLE I

Arterial Concentrations, Arterial-Deep Venous (A-DV) Differences, and Fractional Uptake of Individual Free Fatty Acids across the Forearm

FFA		Arterial concn	A-DV	P*	f‡	b§	P*
		μmoles/liter	*μmoles/liter*				
Myristic	(12:0)	8±1‖	1.5±0.6	<0.02	0.16±0.07	0.36	<0.001
Lauric	(14:0)	15±2	2.8±0.5	<0.001	0.17±0.03	0.24	<0.001
Palmitic	(16:0)	119±8	23.6±3.0	<0.001	0.20±0.02	0.22	<0.01
Palmitoleic	(16:1)	22±2	3.7±0.9	<0.001	0.16±0.04	0.23	<0.05
Stearic	(18:0)	52±3	10.6±1.5	<0.001	0.20±0.03	0.29	<0.01
Oleic	(18:1)	151±13	37.7±5.0	<0.001	0.25±0.02	0.27	<0.001
Linoleic	(18:2)	53±4	8.4±1.6	<0.001	0.13±0.04	0.25	<0.001
Arachidonic	(20:4)	7±0.4	0.1±0.4		0.03±0.06	−0.24	
Total	FFA	427±31	88.4±11.2	<0.001	0.20±0.02	0.24	<0.01

* *P*, probability that the A-DV difference and *b* do not differ from zero.

‡ Fractional uptake calculated as (A-DV)/A.

§ Regression coefficient for the regression of A-DV concentration differences on the corresponding arterial concentration.

‖ Data are presented as mean ±SE, n = 20.

and into the brachial artery in 20 healthy subjects. After a 30 min rest period, duplicate samples were collected from both catheters at the end of a 5 min occlusion of the hand circulation.

In 11 other subjects a No. 7 or 8 Goodale-Lubin catheter was introduced into a medial antecubital vein, advanced under fluoroscopic control to a right-sided hepatic vein, and positioned 3–4 cm from the wedge position. In addition, a brachial artery catheter was inserted percutaneously. Hepatic blood flow was measured using the continuous infusion technique (7) with indocyanine green dye. These 11 subjects were all restudied on another occasion, when blood samples were obtained from a hepatic vein and an artery after the repeated administration of nicotinic acid (NA) during a 1 hr period. The total dose of NA was 1.6 g, 1 g being given intravenously and 0.6 g perorally.

In one additional subject, a Goodale-Lubin catheter was positioned in a right-sided renal vein and catheters were inserted percutaneously into a brachial artery and an antecubital vein. A continuous infusion of albumin-bound oleate-^{14}C (0.6 μCi/min, New England Nuclear Corp., Boston, Mass.) was given intravenously. Starting after 30 min of infusion, four blood samples were obtained during a 30 min period from the artery and the renal vein.

In the five cholecystectomy patients a brachial artery catheter was introduced just prior to the surgical procedure. Halothane and pentobarbital anesthesia was given. After exposure of the portal vein a direct puncture was made and blood samples were collected simultaneously from the portal vein and the brachial artery.

All catheters were kept patent by intermittent flushing with saline without added heparin.

All volunteers and patients were informed of the nature of the study and the risks involved before giving their consent.

Methods. The plasma concentrations of individual FFA were determined using a gas chromatographic method (8, 9). Radioactivity in the FFA fraction was measured as described elsewhere (6). Indocyanine green dye was determined spectrophotometrically at 805 nm in serum samples. Standard statistical methods were employed (10) using the paired *t* test when applicable.

RESULTS

The arterial concentrations of individual FFA and the arterial-deep venous (A-DV) concentration differences across the forearm are given in Table I. There were significant uptakes to the forearm deep tissues for all FFA except for arachidonic acid. The FFA uptake was positively related to the arterial FFA concentration. The fractional uptake (the [A-DV] difference divided by the arterial concentration) did not differ significantly among the acids showing a significant net uptake.

The corresponding data for arterial and hepatic venous FFA concentrations are presented in Table II. Significant arterial-hepatic venous (A-HV) concentration differences were present for all FFA except for arachidonic acid. The fractional uptakes of lauric, myristic, and palmitoleic acid were higher and that of stearic acid was lower than those of the other FFA ($P < 0.01$, Fig. 1). The regressions of (A-HV) differences on arterial concentrations were significant for all acids except stearic and arachidonic acid. The estimated splanchnic blood flow (ESBF) was 1408±135 (mean±SD) ml/min. There was no correlation between ESBF and the fractional uptake of FFA ($r = -0.06$).

When the same subjects were restudied after receiving nicotinic acid (NA), the arterial concentration of FFA averaged about 25% of the concentration on the previous occasion (Table III). The concentrations of the individual FFA were all significantly lower after NA ($P <$

TABLE II

Arterial Concentrations, Arterio-hepatic Venous (A-HV) Differences, and Fractional Uptake of Individual Free Fatty Acids across the Splanchnic Vascular Bed

FFA	Arterial concn	A-HV	P*	f‡	b§	P*
	μmoles/liter	*μmoles/liter*				
12:0	10±1‖	6.7±1.2	<0.001	0.65±0.03	0.81	<0.001
14:0	21±3	12.7±2.2	<0.001	0.59±0.04	0.75	<0.001
16:0	156±17	39.3±6.0	<0.001	0.25±0.02	0.27	<0.01
16:1	28±4	15.4±2.1	<0.001	0.54±0.04	0.51	<0.001
18:0	65±6	6.7±1.5	<0.05	0.11±0.02	0.07	
18:1	208±20	51.4±6.6	<0.001	0.25±0.02	0.22	<0.05
18:2	60±6	19.0±2.7	<0.001	0.32±0.03	0.30	<0.05
20:4	6±1	−0.1±0.3		−0.04±0.07	0.18	
Total FFA	553±54	151.1±19.9	<0.001	0.27±0.02	0.29	<0.01

* *P*, probability that the A-HV difference and *b* do not differ from zero.

‡ Fractional uptake calculated as (A-HV)/A.

§ Regression coefficient for the regression of A-HV differences on the corresponding arterial concentration.

‖ Data are presented as mean ±SE, n = 11.

0.001) with the exception of arachidonic acid. NA had a profound effect on the fatty acid composition of arterial plasma FFA. Thus the percentages of myristic, palmitoleic, and oleic acid decreased, while the relative contributions of palmitic, stearic, linoleic, and arachidonic acid were augmented (Table IV). Significant positive (A-HV) concentration differences were observed for lauric, myristic, and palmitoleic acid after NA, while there was a net release of stearic acid from the splanchnic area (Table III). For the other FFA (as well as for total FFA) the mean (A-HV) differences did not differ from zero. However, significant regressions of (A-HV) differences on arterial concentrations were observed for all acids except arachidonic acid. This regression for total FFA is shown in Fig. 2. The regression line intercepts the x axis at a concentration of about 130 μmoles/liter, which differs significantly from zero ($P < 0.05$). The corresponding intercepts for the regression lines of the individual acids are also given in Table III.

There was a wide range of FFA levels in the five patients in whom arterial and portal venous samples were obtained during surgery (Table V). On the average,

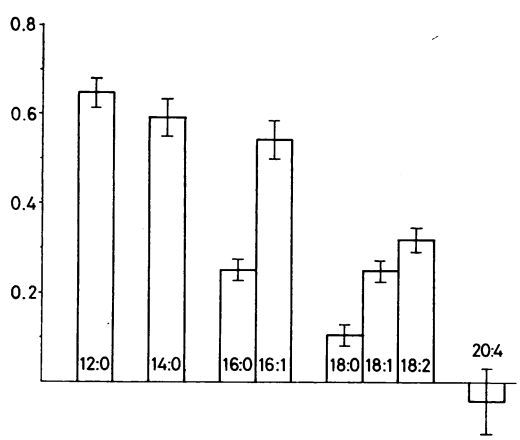

FIGURE 1 Splanchnic fractional uptake of individual FFA in the basal state. Values for lauric (12:0), myristic (14:0), and palmitoleic (16:1) acids were higher and that of stearic acid (18:0) was lower than those of palmitic (16:0), oleic (18:1), and linoleic acid (18:2). No significant net exchange was observed for arachidonic acid (20:4).

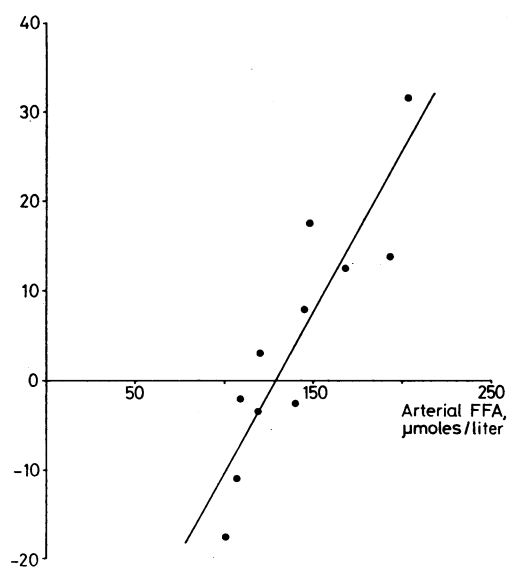

FIGURE 2 Arterial-hepatic venous FFA difference in relationship to the arterial FFA concentration during the administration of nicotinic acid. The intercept of the regression line differs significantly from zero ($P < 0.05$).

TABLE III

Influence of Nicotinic Acid Administration on Arterial Concentration and Splanchnic Exchange of Individual FFA

FFA	Arterial concn	A-HV*	P‡	b§	P‡	x intercepts§	P‡
	μmoles/liter	*μmoles/liter*					
12:0	2.7±0.2‖	0.9±0.3	<0.01	1.13	<0.001	1.9	<0.05
14:0	3.7±0.6	0.8±0.3	<0.05	0.33	<0.05	1.4	
16:0	44.1±3.2	1.1±1.3		0.27	<0.05	39.9	
16:1	4.8±0.8	0.8±0.3	<0.05	0.34	<0.01	2.4	
18:0	22.7±1.7	−1.0±0.4	<0.05	0.15	<0.05	29.2	<0.05
18:1	36.5±3.3	1.2±1.3		0.32	<0.01	32.8	<0.05
18:2	20.8±2.5	1.0±0.8		0.25	<0.01	16.8	<0.05
20:4	5.9±0.5	−0.3±0.5		0.35		6.6	
Total FFA	141.2±10.4	4.6±4.2		0.36	<0.001	128.4	<0.05

* Arterial-hepatic venous difference.

‡ Probability that the A-HV difference, the regression coefficient, and the *x* intercept do not differ from zero.

§ Regression coefficient and *x* intercept for the regression of A-HV difference on the corresponding arterial concentration.

‖ Data are given as mean ±SE, n = 11.

there was a small net release of FFA from the extrahepatic splanchnic tissues, but none of the arterial-portal venous concentration differences deviated significantly from zero.

The arterial-renal venous (A-RV) concentration differences of FFA were small (Table VI) and none of them differed significantly from zero. The (A-RV) differences for oleate-^{14}C were all less than 5% of the arterial level, two being positive and two negative.

DISCUSSION

The arterial-venous concentration difference of plasma FFA across the forearm reflects the combined effects of simultaneous uptake and release of FFA (11, 12). The observed net uptake of 20% of the arterial FFA in the present study is therefore an underestimation of the total FFA uptake. Higher values for the fractional uptake of FFA by resting muscle have been observed in the forearm during inhibition of lipolysis by intraarterial administration of insulin (11) and in the leg using radioactive tracer FFA (13, 14). The observed (A-DV) concentration differences nevertheless indicate that the net exchange of FFA during passage through the forearm muscle is quite similar for each of the individual FFA, except that there is no net exchange of arachidonic acid.

The liver, unlike muscle, does not appear to release FFA into the circulation since the chemical portal-hepatic venous differences agree with those obtained using a radioactive tracer (15). The (A-HV) FFA dif-

TABLE IV

Percentage Composition of the Arterial Plasma Free Fatty Acid Fraction in the Postabsorptive State and after Administration of Nicotinic Acid

FFA	Postabsorptive	After nicotinic acid	P*
12:0	1.8±0.2‡	1.9±0.1	
14:0	3.7±0.2	2.5±0.2	<0.005
16:0	27.8±0.6	31.4±1.0	<0.005
16:1	5.0±0.3	3.3±0.4	<0.005
18:0	12.0±0.5	16.3±0.9	<0.001
18:1	37.6±0.8	25.7±1.1	<0.001
18:2	10.8±0.6	14.5±1.2	<0.02
20:4	1.2±0.2	4.4±0.4	<0.001

* *P*, probability that the change after nicotinic acid is caused by random factors.

‡ Data are given as mean ±SE, n = 11.

TABLE V

*Arterial Concentrations and Arterial-Portal Venous (A-PV) Differences of Individual Free Fatty Acids**

FFA	Arterial concn	A-PV
	μmoles/liter	*μmoles/liter*
12:0	7±2	−0.9±0.7
14:0	21±8	−2.8±1.4
16:0	152±39	−5.3±4.8
16:1	30±10	−3.4±2.1
18:0	58±13	2.6±3.1
18:1	213±59	−6.8±5.0
18:2	73±22	−2.8±1.2
20:4	7±1	0.2±0.9
Total FFA	561±146	−19.2±10.8

* Data are given as mean ±SE, n = 5.

TABLE VI

*Arterial Concentrations and Arterial-Renal Venous (A-RV) Differences of Individual Free Fatty Acids in One Subject**

FFA	Arterial concn	A-RV
	μmoles/liter	*μmoles/liter*
14:0	14±1	2.2±1.0
16:0	180±2	4.5±7.1
16:1	22±1	1.0±1.0
18:0	78±2	−0.9±4.3
18:1	264±4	2.7±7.4
18:2	99±3	−1.1±2.9
Total FFA	657±6	8.4±13.1

* Data are given as mean ±SE, n = 4.

ference in the postabsorptive state is therefore determined by the uptake in the liver and the exchange of FFA across the extrahepatic splanchnic tissues. The latter exchange may include a net release of FFA from omental adipose tissue. To evaluate to what extent the (A-HV) differences were influenced by extrahepatic exchange of FFA, the arterial-portal venous differences of FFA were measured in a group of subjects during abdominal surgery. With a reservation for the possible effect of anesthesia, this exchange seems to be of minor importance (Table V) and does not influence the fatty acid composition of portal venous FFA. Since the arterial FFA levels in these patients were the same as in the group in which the (A-HV) differences were measured, there is no reason to believe that omental FFA release could have been underestimated. It is thus concluded that in the present study (A-HV) differences measure mainly hepatic uptake and probably slightly underestimate this.

The observed splanchnic uptake of 37% of the arterial FFA is similar to that observed earlier in dogs (15–17) and in humans (5). The dependence of hepatic uptake on arterial concentration has also been observed in the dog (18) and in the isolated perfused rat liver (19).

In contrast to the findings for muscle, considerable differences were noted in the fractional uptake of individual FFA in the splanchnic area. Nestel (20) observed that the fractional turnover rate of linoleic acid in man exceeds that of palmitic acid and similar studies in the rat (21–25) have shown that, compared to that of palmitic acid, the turnover rates of lauric, myristic, palmitoleic, and linoleic acids are higher and that of stearic acid lower. The turnover rates of the individual FFA thus seem to vary in the same order as their fractional splanchnic uptake (Fig. 1). The latter rose with decreasing chain length and increasing unsaturation—as observed previously in two individuals (5)—and it is noteworthy that similar differences between the individual acids have been observed with regard to their respective rates of release from adipose tissue in vitro (1). The present results indicate that this pattern of preferential release of short-chain and unsaturated acids from adipose tissue is also present in vivo. The percentages of lauric and myristic acids, for instance, are higher in plasma FFA than in adipose tissue despite the fact that these acids are removed from the plasma by the liver more than twice as effectively as the average FFA. The differences in turnover among the FFA thus seem to be determined mainly by the adipose tissue and the liver, both organs showing a preference for short-chain and unsaturated acids.

When the arterial FFA concentration was lowered by the administration of NA, the hepatic uptake of total FFA decreased to insignificant values, but significant uptakes were still found for lauric, myristic, and palmitoleic acid, while stearic acid was released from the splanchnic area. The regression of (A-HV) differences on arterial concentrations was significant for all FFA except arachidonic acid. Thus, the uptake did not decrease to zero but changed into a release at the threshold concentrations given by the x intercepts of Table III. This release of fatty acids probably comes from the liver since it is not likely to derive from adipose tissue in the splanchnic region. Adipose tissue contains almost 10 times as much oleic as stearic acid (26) and releases oleic acid preferentially, whereas in the present study stearic acid was preferentially released from the splanchnic region.

The administration of NA had a profound effect on the fatty acid composition of the plasma FFA fraction. The percentages of the monounsaturated acids decreased, while those of palmitic, stearic, and linoleic acid increased. Decreasing plasma FFA by means of glucose (25–28) or glucagon administration (29) had similar effects on the fatty acid composition. The concentration of arachidonic acid was unaffected by NA administration, in accordance with observations in the rat (30). Studies on the fatty acid composition of plasma FFA during experimentally induced changes in total FFA have led to the suggestion that part of the plasma FFA derives from pools other than adipose tissue triglycerides (27–29). The present results on (A-HV) FFA differences after NA show that at low FFA levels the liver may contribute to plasma FFA, at least to the concentration of stearic acid, which is relatively high in this situation.

Earlier studies in dogs (31) have indicated that the kidneys do not take up FFA from the circulation, with the possible exception of a small palmitic acid uptake. These observations were confirmed for man in the experiment with renal venous catheterization. No consistent (A-RV) differences were found and this was not due

to a simultaneous uptake and release of FFA since the specific activity of oleate was the same in the artery and the renal vein. These results make it unlikely that the kidneys consume quantitatively significant amounts of plasma FFA. However, the possibility cannot be excluded that circulating FFA are of importance for the intermediary metabolism of the kidneys, since with the high renal blood flow even the observed (A-RV) FFA difference of 8 μmoles/liter—although not statistically significant—could indicate a not inconsiderable net FFA uptake.

Stearic acid differed from the rest of the FFA in that its small hepatic uptake was independent of its arterial concentration. Similar results were obtained by Trout and Estes (32) in rats, no consistent relationship being found between the FFA levels and the fraction of injected stearate-1-^{14}C appearing in the livers. The myocardial uptake of stearic acid has also been shown to be independent of its arterial concentration (4). The percentage of stearic acid in plasma FFA is about twice that in adipose tissue (9, 26) and this difference may be explained at least in part by the low hepatic and myocardial removal of this acid from the plasma FFA.

Plasma free arachidonic acid has an exceptional position among the FFA. Its concentration has been shown to be independent of the total FFA level (9). It did not change when the plasma FFA was lowered by NA. Furthermore, there was no significant uptake of arachidonic acid by liver or muscle. It can be concluded that the regulation of the free arachidonic acid concentration in plasma differs completely from that of the other FFA.

The present data have some implications for the choice of tracer for studies of FFA metabolism. Most investigators in this field have used a single labeled fatty acid as a tracer (usually palmitic acid) and have calculated a total FFA specific activity based on the plasma tracer radioactivity and the total FFA concentration. It would seem preferable that the results instead are expressed as the specific activity of the individual plasma FFA that has actually been labeled by the introduction of the tracer. There are two important reasons for this: (*a*) there are gross differences between the metabolism of the individual FFA, especially in the liver, and results obtained with one tracer acid are therefore not valid for the total FFA fraction; (*b*) since the fatty acid composition of plasma FFA varies with the total concentration (as shown for instance after nicotinic acid in the present study) the errors introduced are not constant and results obtained at different arterial FFA levels are thus not comparable. These difficulties may be avoided by treating each individual FFA as a separate, circulating pool of fatty acids.

These results from tracer experiments will accordingly provide information only about the metabolism of an individual FFA and we are faced with the problem of how to render the data as general as possible without having to introduce multiple tracers, which tend to raise methodological complications. The characteristics of a suitable single FFA tracer should be that it is present in a high concentration in the plasma FFA fraction and that its metabolic behavior is as close as possible to the average plasma FFA. Oleic and palmitic acid seem to fulfill these requirements. They are the acids present in the highest concentrations in the plasma FFA and their fractional uptakes in both muscle and liver are the same as that of total FFA. Oleic acid has the additional advantage that its muscle uptake is also representative of that of total FFA during exercise (6).

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REFERENCES

1. Hollenberg, C. H., and A. Angel. 1963. Relation of fatty acid structure to release and esterification of free fatty acids. *Am. J. Physiol.* **205**: 909.
2. Harris, P., C. Chlouverakis, J. Gloster, and J. Howel Jones. 1962. Arterio-venous differences in the composition of plasma free fatty acids in various regions of the body. *Clin. Sci. (Oxf.).* **22**: 113.
3. Rothlin, M. E., and R. J. Bing. 1961. Extraction and release of individual free fatty acids by the heart and fat depots. *J. Clin. Invest.* **40**: 1380.
4. Carlsten, A., B. Hallgren, R. Jagenburg, A. Svanborg, and L. Werkö. 1963. Myocardial arteriovenous differences of individual free fatty acids in healthy human individuals. *Metab. (Clin. Exp.).* **12**: 1063.
5. Carlsten, A., B. Hallgren, R. Jagenburg, A. Svanborg, and L. Werkö. 1967. Arterio-hepatic venous differences of free fatty acids and amino acids. Studies in patients with diabetes or essential hypercholesterolemia, and in healthy individuals. *Acta Med. Scand.* **181**: 199.
6. Hagenfeldt, L., and J. Wahren. 1968. Human forearm muscle metabolism during exercise. II. Uptake, release and oxidation of individual FFA and glycerol. *Scand. J. Clin. Lab. Invest.* **21**: 263.
7. Bradley, S. E. 1948. Measurements of hepatic blood flow. *Methods Med. Res.* **1**: 199.
8. Hagenfeldt, L. 1966. A gas chromatographic method for the determination of individual free fatty acids in plasma. *Clin. Chim. Acta.* **13**: 266.
9. Hagenfeldt, L. 1968. The concentrations of individual free fatty acids in human plasma and their interrelationships. *Ark. Kem.* **29**: 57.
10. Snedecor, G. W., and W. G. Cochran. 1967. Statistical Methods. Iowa State University Press, Ames. 6th edition.
11. Rabinowitz, D., and K. L. Zierler. 1962. Role of free fatty acids in forearm metabolism in man. quantitated by use of insulin. *J. Clin. Invest.* **41**: 2191.
12. Hagenfeldt, L., and J. Wahren. 1966. Simultaneous uptake and release of individual free fatty acids in human forearm muscle during exercise. *Life Sci.* **5**: 357.

13. Havel, R. J., B. Pernow, and N. L. Jones. 1967. Uptake and release of free fatty acids and other metabolites in the legs of exercising men. *J. Appl. Physiol.* **23**: 90.
14. Hagenfeldt, L., B. Pernow, and J. Wahren. 1971. Metabolism of free fatty acids during exercise in patients with occlusive arterial disease of the leg. *In* Muscle Metabolism during Exercise. B. Pernow and B. Saltin, editors. Plenum Publishing Corporation, New York. 505.
15. Basso, L. V., and R. J. Havel. 1970. Hepatic metabolism of free fatty acids in normal and diabetic dogs. *J. Clin. Invest.* **49**: 537.
16. Fine, M. B., and R. H. Williams. 1960. Effect of fasting, epinephrine and glucose and insulin on hepatic uptake of nonesterified fatty acids. *Am. J. Physiol.* **199**: 403.
17. Spitzer, J. J., H. Nakamura, S. Hori, and M. Gold. 1969. Hepatic and splanchnic uptake and oxidation of free fatty acids. *Proc. Soc. Exp. Biol. Med.* **132**: 281.
18. McElroy, W. T., Jr., W. L. Siefert, and J. J. Spitzer. 1960. Relationship of hepatic uptake of free fatty acids to plasma concentration. *Proc. Soc. Exp. Biol. Med.* **104**: 20.
19. Aydin, A., and J. E. Sokal. 1963. Uptake of plasma free fatty acids by the isolated rat liver: effect of glucagon. *Am. J. Physiol.* **205**: 667.
20. Nestel, P. J. 1965. Metabolism of linoleate and palmitate in patients with hypertriglyceridemia and heart disease. *Metab. (Clin. Exp.)*. **14**: 1.
21. Göransson, G., and T. Olivecrona. 1964. The metabolism of fatty acids in the rat. I. Palmitic acid. *Acta Physiol. Scand.* **62**: 224.
22. Göransson, G. 1965. The metabolism of fatty acids in the rat. IV. Stearic acid. *Acta Physiol. Scand.* **63**: 423.
23. Göransson, G. 1965. The metabolism of fatty acids in the rat. V. Palmitoleic acid. *Acta Physiol. Scand.* **63**: 428.
24. Göransson, G. 1965. The metabolism of fatty acids in the rat. VII. Linoleic acid. *Acta Physiol. Scand.* **64**: 204.
25. Göransson, G. 1965. The metabolism of fatty acids in the rat. VIII. Lauric acid and myristic acid. *Acta Physiol. Scand.* **64**: 383.
26. Hirsch, J. 1965. Fatty acid patterns in human adipose tissue. *Handb. Physiol. Adipose Tissue.* 181.
27. Nakamura, H., G. Faludi, and J. J. Spitzer. 1967. Changes of individual free fatty acids during glucose tolerance test. *Diabetes.* **16**: 175.
28. Warembourg, H., G. Biserte, G. Sezille, J. Jaillard, and M. Bertrand. 1968. Influence du glucose sur la composition des acides gras non estérifiés du plasma humain normal. *Clin. Chim. Acta.* **22**: 349.
29. Warembourg, H., G. Biserte, J. Jaillard, and G. Sezille. 1970. Variations quantitatives et qualitatives des acides gras non estérifiés et des triglycerides circulants induites par le glucagon. *Clin. Chim. Acta.* **28**: 103.
30. Meinertz, H., and V. P. Dole. 1960. Changes in the composition of plasma non-esterified fatty acids after insulin, glucose, and nor-epinephrine. *Fed. Proc.* **19**: 228.
31. Gold, M., and J. J. Spitzer. 1964. Metabolism of free fatty acids by myocardium and kidney. *Am. J. Physiol.* **206**: 153.
32. Trout, D. L., and E. H. Estes, Jr. 1962. Factors affecting liver uptake of serum free stearic acid-1-C^{14}. *Am. J. Physiol.* **203**: 1024.