review

The usefulness of dietary medium-chain triglycerides in body weight control: fact or fancy?[1]

André C. Bach,[2,*] Yves Ingenbleek,[†] and Anny Frey[**]

CEPE, CNRS;* Département des Sciences de l'Aliment, Université Louis Pasteur;[†] and Clinique Médicale A,** Hôpitaux Universitaires, Strasbourg, France

Abstract Compared to long-chain triglycerides (LCT), medium-chain triglycerides (MCT) display some specific physico-chemical, and biological characteristics. Thus, MCT are currently used in clinical nutrition as energy-yielding substrates, and have been advocated for three decades as a useful mean for body weight reduction. This review encompasses most aspects of MCT metabolism arguing this slimming hypothesis pro and con. Findings in support of the opinion (lower energy density, control of satiety, rapid intrahepatic delivery and oxidation rates, poor adipose tissue incorporation) may be invalidated by counteracting data (stimulation of insulin secretion and of anabolic-related processes, increased de novo fatty acid synthesis, induced hypertriglyceridemia). The balance between these two opposing influences depends on the composition (energy intake, nature of ingredients, MCT/LCT ratio, octanoate/decanoate ratio) and duration of the regimen. Due to the high energy level (around 50%) of MCT necessary to achieve body weight loss, long-term compliance to such slimming regimens is unlikely in human nutrition.—**Bach, A. C., Y. Ingenbleek, and A. Frey.** The usefulness of dietary medium-chain triglycerides in body weight control: fact or fancy? *J. Lipid Res.* 1996. **37:** 708–726.

Supplementary key words dietary fats • long chain triglycerides • digestion • absorption • transport • oxidation • storage • obesity prevention/treatment

In westernized countries, relative adiposity is an important health problem affecting a sizable proportion of individuals (1) with normal or minimally elevated body weight who intend to prevent any further weight gain or who decide to counteract the detrimental health consequences of declared obesity. For the sake of attaining these objectives, patients follow a wide set of preventive or therapeutic means, taken alone or in combination. Amongst these approaches, dietary restrictions involving lipids are recognized as being of utmost importance. The large bulk of fatty acids found in usual western diets consists of molecules comprising 12 and more carbon atoms. These long chain fatty acids (LCFA), either saturated or unsaturated, originate from the long chain triglycerides (LCT) provided by vegetable and/or animal oil and fat sources. They contribute to the supply of energy and fulfill the essential fatty acid (EFA) requirements. Although LCT and LCFA show significant differences in their molecular structure and consequently in their biological properties, for this report we will consider that they belong to a unique class of compounds. In contrast, medium chain triglycerides (MCT) yield medium chain fatty acids (MCFA) ($C_{6:0}$, $C_{8:0}$, $C_{10:0}$) upon hydrolysis, and cover only modestly the dietary human energy requirements because they are rarely found in natural products. Starting in the 1950s, it became possible to increase significantly the MCFA content of customary diets by the supply of MCT, a semi-synthetic oil whose fatty acids are constituted almost only of octanoic and decanoic acids (2, 3).

MCT and MCFA reveal distinct physico-chemical and metabolic properties when compared to LCT and LCFA (4). Schematically, the former lipids either follow specific and shorter pathways or undergo more rapidly the same converting steps as those taken by the latter. As a result, MCT appear as an unconventional fat (5, 6) and are proposed for use either in oral/enteral nutrition (4, 7) when the digestion, absorption, or transport of LCT is impaired or in parenteral nutrition (8) when a rapid energy supply is desired. These aspects are in keeping with studies showing that the fatty acids delivered by MCT are abundantly oxidized and poorly stored within tissues. As a logical application of these observations, the claim that MCT formulas might contribute to the

---

Abbreviations: EFA, essential fatty acids; LCFA, long-chain fatty acids (number of carbon atoms ≥ 12); LCT, long-chain triglycerides; LPL, lipoprotein lipase; MCFA, medium-chain fatty acids (6 ≤ number of carbon atoms ≤ 10); MCT, medium-chain triglycerides; RQ, respiratory quotient; TG, triglycerides; TEF, thermic effect of food; VLDL, very low density lipoproteins.

[1]We dedicate this paper to the memory of Vic Babayan, a pioneer in the field of MCT development and research.

[2]To whom correspondence should be addressed at: Centre d'Ecologie et Physiologie Energétiques, CNRS, 23 rue Becquerel, 67087 Strasbourg, France.

control of body weight in human subjects has been repeatedly emphasized over the last decades (5, 9–17), more especially as MCT were regarded as "light fats" (18) and even as "fatless fats" (10, 19).

The accretion of lipids is a physiological process accompanying normal growth from conception to adulthood. It is now unambiguously stated that obesity is the net result of a disrupted balance between energy intake and energy output (20), the excess being stored as triglycerides (TG) in the adipose tissue. These alterations of fat body mass are the primary determinant of changes in total body weight. Most studies performed in the obese indicate that the body has limited ability to oxidize lipids eaten in excess (20). As a result, the storage of body fat stands in direct correlation with the overall energy intake (21), and more specifically with its lipid component (22).

The aim of the present article is to perform a critical assessment of some salient aspects of MCT metabolism, mainly those liable to interfere with the control of body weight. The review will address in succession physiopathogenic aspects of MCT intake, digestion, transport, storage, and oxidation.

REGULATION OF ENERGY INTAKE

The reduction of body weight is invariably associated with the need to reduce dietary energy, and mainly its lipid component. From this point of view, MCT manifest two different promising features. First, on a molecular basis, and due to their shorter chain length, the energy density of MCFA is less than that of LCFA (**Table 1**) (23), although this aspect is overlooked in current applications.

Second, MCT are endowed with satiating properties involving a cascade of preabsorptive and postabsorptive mechanisms. Among preabsorptive satiating factors, smell and taste need to be considered first. MCT are a thin, light yellow, clear, and odorless oil, with a nearly neutral or slightly bland taste, whereas MCFA are characterized by an odor of goat and strong bitterness (hence the common names of caproic, caprylic, and capric acids given to these compounds). This repulsive quality is extremely strong, as a concentration of 0.1% makes a meal unfit for human consumption (6). If MCT manifest refractoriness to hydrolytic and oxidative processes, they undergo rapid cleavage in the presence of acidic dietary components or lipases (5, 6, 24). Such hydrolytic degradation is possible during the storage and disposal time of the experimental mixed diet. One can question whether all necessary measures to prevent such deterioration have always been taken in the past. Moreover, because lingual lipase is extremely active on MCT (25), its responsibility in their early degradation during the chewing time cannot be totally ruled out. Such a hydrolysis could explain the spontaneous behavior of rats choosing the diet containing the smaller proportion of fat when presented with 15% and 25% MCT admixtures, whereas the opposite trend is clearly observed with comparable LCT regimens (26). There is no preferential selection of LCT versus MCT when the diet is given by gastric tubing (27). Palatability must also be regarded as a critical determinant or feeding behavior. As a result of differences between the viscosity of MCT (25–30 cPoises) and of LCT (65–75 cPoises) (24), the palatability of the former is less than that of the latter (28, 29). Humans are nevertheless unable to distinguish MCT from corn oil in mixed flavored drinks (30).

The next step is gastric emptying, usually more rapidly achieved after MCT and MCFA than after LCT and LCFA (31–33), although there is some disagreement on this (34, 35). Food intake stimulates the secretion of gastrointestinal mediators that contribute to the preabsorptive satiating events (35). One of the most studied signals is cholecystokinin, providing divergent results (33, 36–38) that could be, in part, explained by interspecies differences. Moreover, the administration of a cholecystokinin receptor antagonist did not alter food intakes caused by MCT (39, 40), suggesting that other mechanisms must intervene.

The postabsorptive components modulating satiety comprise several circulating mediators originating from the liver and released in the extracellular fluids (41), among which are nonesterified fatty acids, glycerol (42, 43), ketone bodies (42, 44), and above all glucose. The hepatic production of ketone bodies is substantially increased after MCT compared to LCT (see Oxidation

TABLE 1. Effect of fatty acid chain length on their oxidative characteristics

Fatty Acid	Molecular Mass	Heat of Combustion[a] kJ/g	Heat of Combustion[a] kcal/g	CO_2/O_2 Ratio
C16:0	256.4	39.17	9.36	0.696
C10:0	172.3	35.52	8.49	0.714
C8:0	144.2	33.35	7.97	0.727

$C_{16:0}$-CoA + 23 O_2 + 131 (ADP + Pi) → 16 CO_2 + 146 H_2O + 131 ATP + CoA
$C_{10:0}$-CoA + 14 O_2 + 80 (ADP + Pi) → 10 CO_2 + 89 H_2O + 80 ATP + CoA
$C_{8:0}$-CoA + 11 O_2 + 63 (ADP + Pi) → 8 CO_2 + 70 H_2O + 63 ATP + CoA

[a]Data calculated according to Livesey and Elia (23).

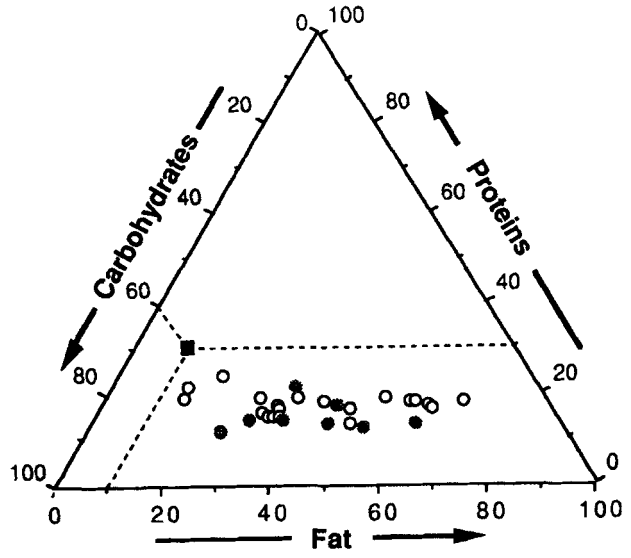

Fig. 1. Effect of MCT (versus LCT) on dietary intake by laboratory animals (mostly rats). Each point, determined by the intersection of three coordinates indicating the proportion (% kcal) of macronutrient classes, represents the result of one study. The black square gives a theoretical example (Fat, 10%; proteins, 30%; carbohydrates, 60%). Data are derived from the following references: (3, 26, 44, 55–61, 73–76, 99, 135–137, 142, 152, 154, 163–165, 211). Black circles: the intake of MCT-fed animals is lower than that recorded in LCT-fed controls. Open circles: the dietary intake is identical in both MCT and LCT experiments. This figure shows that in most instances the replacement of LCT by MCT does not result in a reduction of dietary intake.

of MCFA section). However, this production slackens over time, explaining why the satiating properties triggered by ketone bodies progressively regress, with no differences between protracted use of MCT and LCT (45). Hypoglycemia resulting from depleted glycogen stores is also regarded as a food-craving factor (46). Here too, LCT and MCT behave differently. Compared to LCT, a single oral load of MCT causes a mild hypoglycemia (47–49) proportionate to the amount of ingested oil (50). The likely explanation is a slight hyperinsulinemic response (28, 47–52) attributed to direct stimulatory effects of MCFA (47, 53) and/or of ketone bodies (54) on β-cell islets. Some authors hold the view that hyperinsulinemia and hypoglycemia are closely interwoven events following MCT long-term intake (50, 55–57). Others claim (12, 16, 58), notably in the Zucker rat (59, 60), that both circulating parameters are not influenced by MCT loading. In fact, their evolutionary patterns seem time-dependent (45, 61). All studies conclude that glucose tolerance is improved after MCT administration (62–64) as a higher glucose supply is required for the maintenance of euglycemia during intravenous insulin infusion (16, 65). With MCT intake, a reduction in hepatic glucose output is observed (66, 67) likely to result from the exhaustion of hepatic glycogen reserves (68) and from reduced availability of gluconeogenetic precursors (43). At the same time, turnover rate studies have shown that the plasma glucose disappearance curve, as well as the peripheral tissue glucose uptake, are enhanced (65, 69), stimulating the production of malonyl-CoA and thus de novo fatty acid synthesis.

Piecing these data together, the feeling of satiety appears to be the result of a cascade of interacting impulses ultimately integrated within regulatory sensors of the central nervous system (70). Some events, such as accelerated gastric emptying and declining glycemia, would cause a reduction in anorectic sense and in meal intervals, whereas the above-mentioned mediators would favor their prolongation. The respective importance of these two opposing influences presumably shifts the scale and explains the disparity of behavioral responses. In any event, short-term experiments uphold the view that MCT have satiating properties (27, 35, 39, 40, 71, 72), trioctanoate being much more effective than tridecanoate. When regimens are administered during long-term trials, only a few working groups still record a reduction in food intake with MCT versus LCT (**Fig. 1**) (55, 56, 59, 60, 73–76).

TOLERANCE

In the United States, MCT benefit from the GRAS (generally regarded as safe) label provided for oral/enteral use by the Food and Drug Administration, confirming the good tolerance of MCT in human nutrition. Recommended dietary allowances for healthy adults range from 30 to 100 g, covering up to 40% of the daily energy requirements (29, 52, 77, 78). However, adverse symptoms are commonly described—nausea, vomiting, bloating, emesis, gastrointestinal discomfort, abdominal cramps, osmotic diarrhea—following a too large or not progressive enough incorporation in the diet of healthy volunteers or patients (28–30, 33, 52, 65, 77, 79). Temporary interruption and progressive restarting of the MCT regimen may be necessary (28, 78), and the tolerance improves over time in most instances (65, 78).

The oral administration of MCT leads to the appearance of MCFA among the plasma nonesterified fatty acids (49, 80–82). In healthy subjects ingesting approximately 50 g MCT in a 1000-kcal equilibrated diet, the concentrations of $C_{6:0}$–$C_{12:0}$ reach plasma levels of 200–250 μmol/L (82). After this postprandial peak, the plasma concentration of nonesterified fatty acids returns rapidly to the initial values (81–85). The presence of MCFA in the blood has often been considered responsible for deleterious consequences. Substantial quantities of MCFA and shorter fatty acids are found in the blood during metabolic or toxic encephalopathy accom-

panying hepatic insufficiency and impairment of lipid metabolism (86, 87). These latter disorders, associated with those induced by protein catabolites, likely account for the seriousness of the encephalopathy much more than the circulating MCFA as such.

In cirrhotic subjects, especially in those with porto-caval shunt, an oral/enteral MCT load causes an accumulation in the blood of unbound (to albumin) octanoic acid (80, 83). Octanoate is also recovered in both ascitic and cerebrospinal fluids at the same time as neurological troubles may develop. Rapidly released in the intestine, the MCFA follow the portal route (see following section), bypass the liver by the porto-caval anastomoses, and are massively discharged into the circulation. MCFA have a weak binding affinity for albumin (88) and may cross the blood–brain barrier to diffuse into the cerebrospinal fluid when the binding capacity is overwhelmed. In cirrhotic subjects enterally fed with MCT, no development of encephalopathy has been described (89, 90). Nevertheless, the risk of detrimental consequences on brain function cannot be totally excluded in patients undergoing acute liver failure and/or hypoalbuminemia (7), conditions scarcely found in obesity. We will develop later (see oxidation of MCFA section) the role of ketone bodies and dicarboxylic acids released as end-products of MCT catabolism.

TISSUE PARTITION OF EXOGENOUS FAT

It has been amply demonstrated that the digestive bioavailability of MCT is greater than that of LCT. Compared to LCT, MCT hydrolysis starts in the stomach (91–93), is faster and more complete (94, 95), their gastric transit quicker (31–33), their absorption achieved more proximally, more rapidly (93, 96), and more efficiently (74, 97–101). These differences at the intraluminal level are quantitative and their consequences are relatively minor. In contrast, transport systems elicit qualitative characteristics with much greater consequences.

Partition between liver and extrahepatic tissues

The chylo-portal distribution of the exogenous fatty acids as function of their chain length (96, 102) has an essential influence on their subsequent behavior in the organism (**Fig. 2**). According to established views, LCFA leave the intestine by the lymphatic pathway, after their incorporation into chylomicron-TG (103). The bulk of these chylomicrons undergoes intravascular hydrolysis to yield most of the LCFA to extrahepatic tissues, while the remaining fraction is transported to the liver. The LCFA reach the liver as albumin-bound fatty acids (after enzymatic cleavage of chylomicrons and chylomicron remnants) or as TG (after chylomicron-remnant endocytosis) undergoing hydrolysis by lysosomal triglyceride-lipase. On the other hand, MCFA, totally released by digestive enzymes, follow the portal vein, weakly bound to albumin. Their uptake by the liver reaches from 80 to 100% of the whole portal flux (84), with the remaining fraction discharged into the bloodstream and becoming available to peripheral tissues.

This stringently defined framework needs to be modulated, as all fatty acids use both portal and lymphatic transport systems in varying proportions (91, 104–106): The longer the fatty acids are, the more they are found in the lymph and the less in the portal blood; in the lymph, they circulate as chylomicron-TG; in the portal blood, they are in the form of fatty acids bound to albumin (107). Thus, 8% of MCFA are found in the chylomicron-TG 3 h after ingestion of a meal including MCT by healthy subjects (108). After 6 days on such a regimen, the proportion rises to 15%. The simultaneous administration of MCT and LCT augments the concentration of MCFA in the lymph (109, 110). Finally, it has been observed in the rat intestinal mucosa that MCT administration induces an increase in MCFA acylation processes (111), which suggests an augmented fatty acid incorporation into lipids synthesized by the intestine. In fact, increasing the concentration of circulating TG-incorporated MCFA, as has been demonstrated in tripelargonin-fed rats with porto-caval shunts, results in an enrichment of the adipose tissue in these fatty acids (112).

Previous workers have considered that the metabolic fate of MCFA is confined almost exclusively within the liver (104). Later, Wells (106) claimed that peripheral tissues are involved predominantly. In agreement with Rebouche, Panagides, and Nelson (113), one can say that the vast majority, but not all MCFA, undergo intrahepatic bioconversion. However, the slight and progressive rise of MCFA in the lymphatic circulation and the associated decline of ketonemia (see oxidation of MCFA section) as the MCT-regimen is prolonged suggest that extrahepatic tissues play increasingly important roles in the behavior of MCFA with time.

Partition between storage and oxidative tissues

Another factor intervening in the tissue distribution of exogenous lipids is that of lipoprotein lipase (LPL) (114). This enzyme is located on the endothelial wall of the vessels irrigating the muscles, major site for fatty acid oxidation, and the adipose tissue, major site for fatty acid storage (115). The rate of TG uptake is proportional to the LPL tissue activity (116): elevated in the skeletal muscle under fasting conditions and in the adipose tissue in the postprandial period. Because of this reciprocal relationship, the LPL drives the TG-incorporated

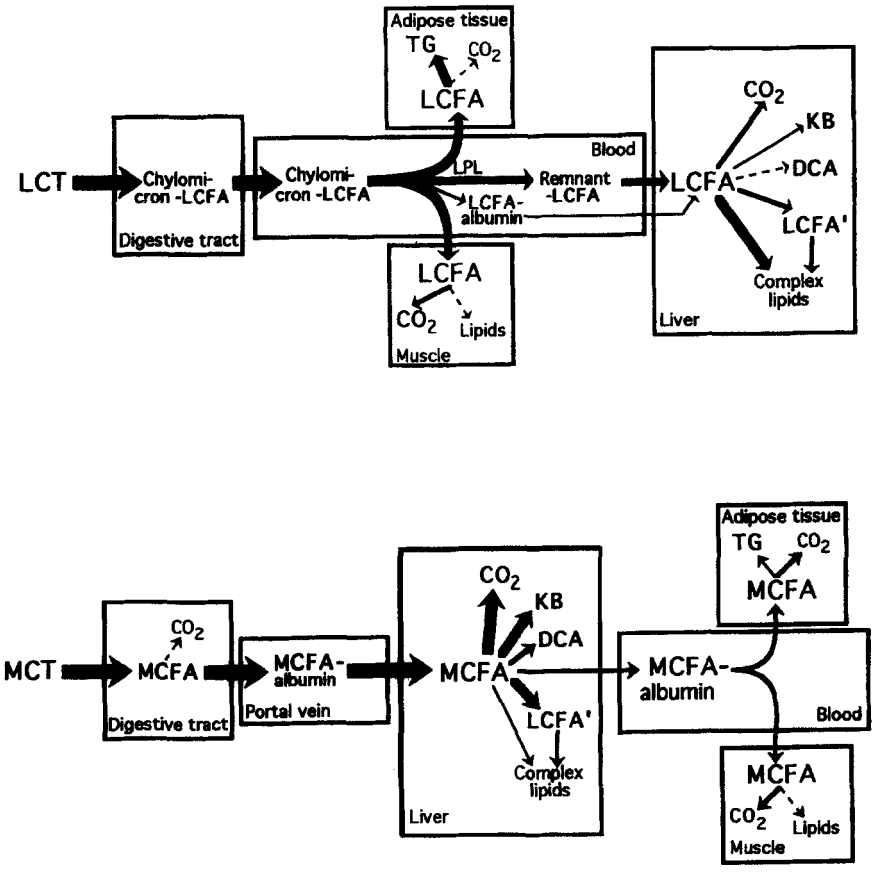

Fig. 2. Transport, distribution, and metabolic fate of exogenous fatty acids according to their chain length. DCA, dicarboxylic acids; KB, ketone bodies; LCFA, long-chain fatty acids; LCFA', de novo synthesized, elongated and/or unsaturated LCFA; LCT, long-chain triglycerides; LPL, lipoprotein lipase; MCFA, medium-chain fatty acids; MCT, medium-chain triglycerides; TG, triglycerides. The width of the arrows reflects the relative importance of the pathway.

fatty acids towards muscle or adipose tissue, e.g., towards a different metabolic fate, oxidation or storage (Fig. 2). In obesity, a lowered LPL activity in the muscle and an increase in the adipose tissue (59, 117) contribute to stimulate fat storage. Finally, the higher activity of adipose tissue LPL in obese patients on very low-calorie diets (118) would tend to make the body refractory to further weight loss.

These processes essentially concern LCFA, whose principal forms of transport are the chylomicron- and VLDL-TG and their remnants, and much less the MCFA, which are poorly incorporated into these lipoproteins (119). Moreover, it is shown that a MCT-based diet leads to a lower adipose tissue LPL activity in the obese Zucker rat than that observed after an LCT regimen (59).

Partition between cytosol and mitochondrion

The hydrophobic properties of LCFA imply that specific transport systems are required for their intracellular delivery. A class of cytosolic proteins, the fatty acid-binding proteins, fulfill this transport task from the cell membrane to the target organelles. LCFA bind quickly and easily to these fatty acid-binding proteins (120), the prerequisite step to reach the enzyme localization sites and to undergo rapid activation into acyl-CoA. On the other hand, the water-soluble MCFA are minimally bound to fatty acid-binding proteins (121, 122), which explains their low conversion rate into acyl-CoA (123).

An additional specific carrier mechanism occurs at the wall of the mitochondrial inner membrane. The essential role played by carnitine as LCFA transporter arose from work on the rat liver (124). It was shown later that intramitochondrial entry of MCFA was carnitine-independent (125). More recent studies, however, have brought to light that this independence is only partial (113, 126). In the liver, about 10–20% of octanoate is transported as acyl-carnitine (127, 128), whereas in muscle MCFA are totally dependent on the shuttling activity of carnitine (129).

As a result of distinct plasma and intracellular trans-

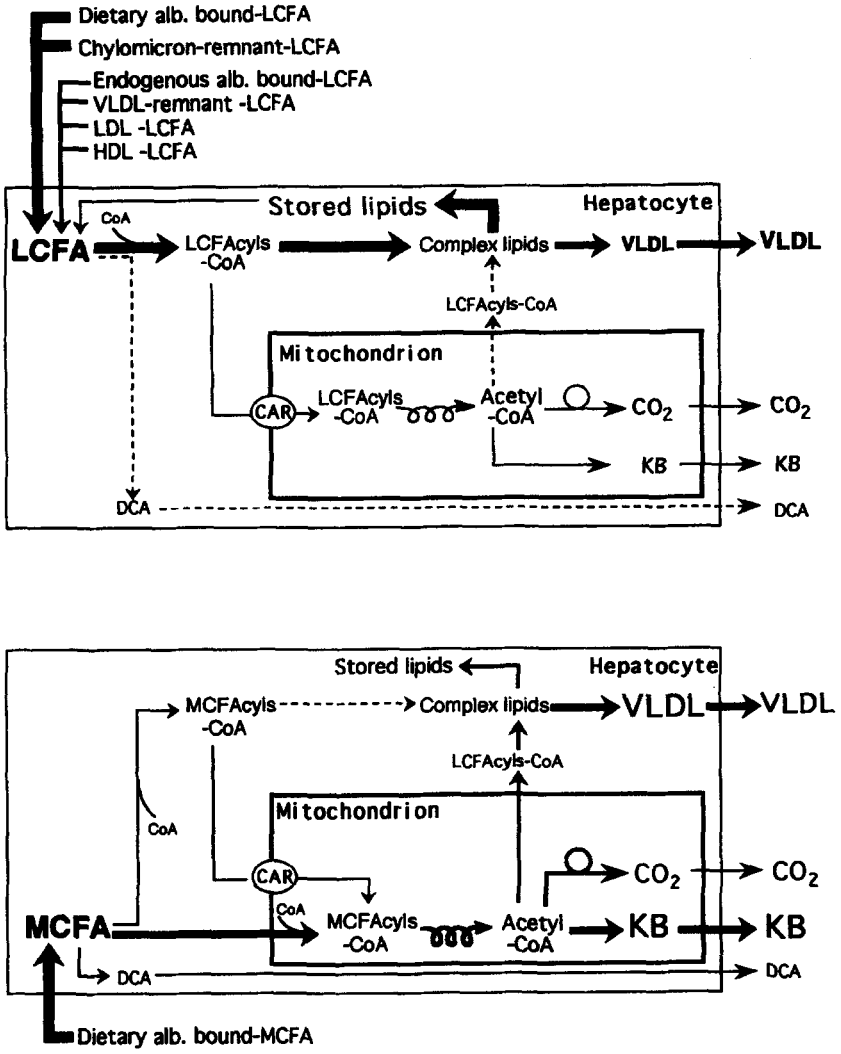

Fig. 3. Metabolic pathways of exogenous fatty acids in the hepatocyte according to their chain length. Alb., albumin; CAR, carnitine; CoA, coenzyme A; DCA, dicarboxylic acids; HDL, high density lipoproteins; KB, ketone bodies; LCFA, long-chain fatty acids; LDL, low density lipoproteins; MCFA, medium-chain fatty acids; VLDL, very low density lipoproteins. The width of the arrows reflects the relative importance of the pathway.

port systems, the two types of lipids will reach different tissues and undergo separate metabolic fates, namely incorporation into complex lipids or oxidation.

INCORPORATION OF EXOGENOUS MCFA INTO COMPLEX LIPIDS

Incorporation of MCFA as such

Single loads (81, 130) and in vitro experiments (130–133) have clearly shown that the incorporation of MCFA per se into liver TG is low and less than that of the LCFA (**Fig. 3**). Moreover, MCFA are not incorporated into liver phospholipids (130, 131, 133). The incorporation of dietary MCFA does not exceed a few percent of intake whatever the elapsed time (91, 134–137). The storage of $C_{10:0}$ is slightly more elevated than that of $C_{8:0}$ (138). It even appears that the tissue uptake of MCFA tends to decrease as the MCT-regimen is maintained (61). It is interesting to observe that obese Zucker rats store more MCFA in their liver than non-obese counterparts (138).

In the adipose tissue, MCFA are virtually absent and only detectable after dietary supplementation (112, 135, 136, 139, 140). As shown in hepatocytes, MCFA are less incorporated into adipocyte TG than LCFA (**Fig. 4**) (115, 141). The incorporation of $C_{8:0}$ is 5 to 20 times less efficient than that of $C_{10:0}$ (61, 112). After 3 months on MCT regimen, Hill et al. (61) found less than 9% MCFA

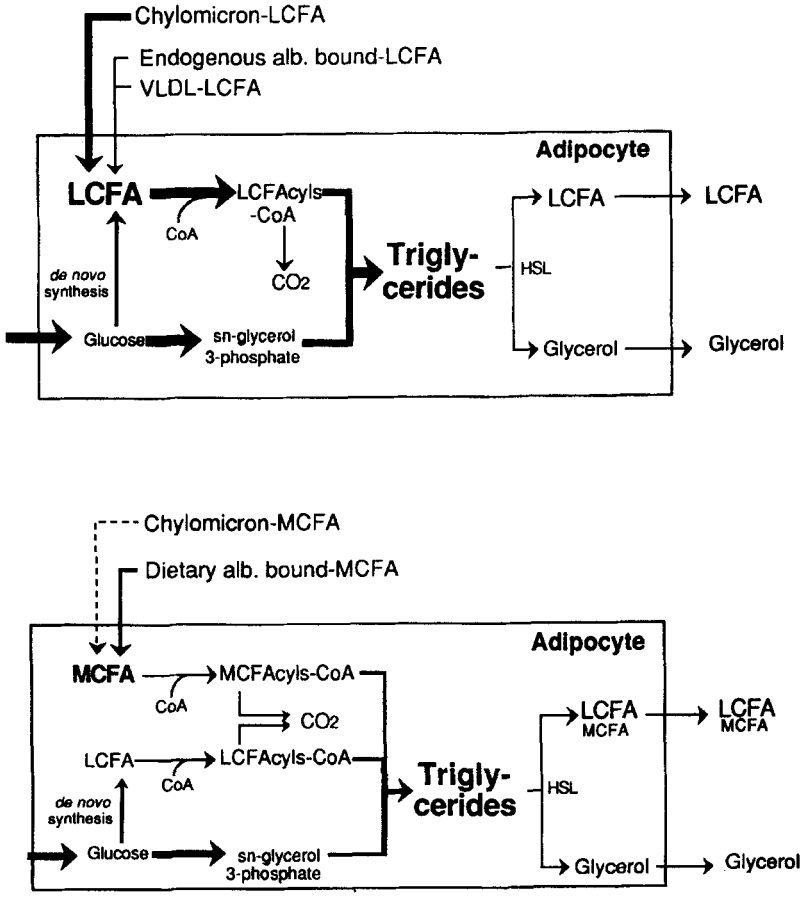

Fig. 4. Metabolic pathways of fatty acids in the adipocyte according to their chain length. Alb., albumin; CoA, coenzyme A; HSL, hormone-sensitive lipase; LCFA, long-chain fatty acids; MCFA, medium-chain fatty acids; VLDL, very low density lipoproteins. The recycling of released fatty acids is not shown. The width of the arrows reflects the relative importance of the pathway.

in several adipose tissues of non-obese volunteers, although these fatty acids represented 93% of the dietary fatty acids. Here, too, accumulation of MCFA as such went down as the regimen was prolonged (61). The simultaneous supply of MCFA and LCFA to rat adipocytes relatively depresses the incorporation of MCFA without modifying that of LCFA (141). It is worth mentioning that TG synthesis appears up-regulated in obese Zucker rats maintained on an MCT-regimen, due to a higher incorporation of MCFA in the adipose tissue (138, 142).

De novo synthesis, elongation, and desaturation of fatty acids

Liver studies have shown that a large proportion of radiolabeled MCFA was recovered in newly synthesized LCFA (132, 143). Results obtained in fasted fructose-refed rats or in human subjects also indicate that MCFA can be partially retailored to LCFA before their storage (82, 144). Many authors have studied the de novo fatty acid, exclusively LCFA, synthesis in relation to the nature of the dietary lipids (49, 134, 145–148). It is now universally recognized that this pathway is down-regulated when a fat-poor diet is shifted to a fat-rich one, and that MCT operate less efficiently. In other words, de novo fatty acid synthesis is less depressed by an MCT-regimen than by an LCT-regimen.

Acetyl-CoA carboxylase, key enzyme of fatty acid synthesis, is inhibited by physiological concentrations of long-chain fatty acyl-CoA, but not by medium-chain fatty acyl-CoA (149). It is activated by citrate (150). When LCT are replaced by MCT, the reduced disposal of long-chain fatty acyl-CoA reinforces the effects generated by the increased MCT-dependent production of citrate (151). Malonyl-CoA, the end-product of acetyl-CoA carboxylase stimulation, is present in larger quantities after an MCT than after an LCT diet (147), with an enzymatic activity reportedly enhanced in the former condition (58–60, 73, 152–156). The situation is similar for the fatty acid synthetase (154, 155) and for the other en-

zymes playing contributory roles (45, 57, 58, 60, 137, 152, 154). The MCT-induced increase in lipogenic enzyme activities is positively correlated with the amount of MCT provided by the diet (73).

Some investigators (134) hold that the enzymes implicated in elongation and desaturation processes are more stimulated by MCT versus LCT regimens, but others (138, 157) express the opposite opinion. Nevertheless, experiments using rat liver mitochondria reveal clear-cut preferential affinities for the elongation of MCFA (158), whereas desaturating processes more specifically concern fatty acids with 14 or more carbon atoms (159).

In the adipose tissue, de novo fatty acid synthesis represents only a minor contribution to lipid accretion (160) (Fig. 3). Those peculiarities, already described in the liver, are also found here: inhibition of acetyl-CoA carboxylase by the long-chain fatty acyl-CoA and its activation by citrate (161); lower efficiency of MCFA than LCFA in depressing the lipogenic-enzyme expression (155); preservation of a higher de novo synthesis rate during an MCT regimen (58), even in the obese Zucker rat (138, 142).

Liver and blood lipids

What are the consequences of a reduced MCFA incorporation and an accelerated LCFA de novo synthesis on the final liver lipid content? Once again, opinions are divergent (60, 99, 162, 163), but it seems that a smaller lipid accumulation is observed in the liver after an MCT-based regimen (45, 97, 134, 164, 165). Such a diminished lipid accretion is also recorded after experimental alcoholic cirrhosis in the rat: isocaloric substitution of LCT by MCT markedly reduces the ability of ethanol to produce a fatty liver (131). Moreover, preexisting steatosis (166) and lipodystrophic hepatomegaly (64) regressed under MCT feeding.

Part of the lipids synthesized within the hepatocytes are released into the bloodstream as VLDL (167) (Fig. 3). This has been observed when fatty acids are added to the rat liver perfusion medium, MCFA being noticeably less efficient than LCFA (119, 168). In long-term experiments, the situation is altered in such a way that increased triglyceridemia appears as a direct consequence of MCT intake. This has been demonstrated in animal studies (56, 59, 61, 134, 165) as well as in human surveys (65, 82, 169–171). The hypertriglyceridemia is explained by a reduced LPL activity in peripheral tissues (59) and by alterations in the partitioning of newly synthesized TG. When fatty acids are mainly of extrahepatic origin, as after LCT ingestion, the synthesis of VLDL is reduced and the TG synthesized by the liver accumulate in the cytosol (167). In contrast, the intake of MCT accelerates the fatty acid synthesis, as well as the production and secretion of VLDL (165), with a concomitant decrease in tissue lipid storage. These VLDL incorporate up to 10% MCFA in their TG, as documented in fasting subjects overfed for 6 days with MCT (82).

OXIDATION OF MCFA

In all tissues, mitochondria are the main oxidative sites of MCFA, whereas peroxisomes are not or are minimally involved unless huge amounts of MCFA are available (172). While the activation of the MCFA can occur in the cytoplasm (173), it takes place mostly in the mitochondrial matrix where a medium-chain acyl-CoA synthetase has been found (123). The oxidation rate of the MCFA is faster and greater than that of the LCFA (81, 85, 131, 132, 148, 174, 175). Preferential oxidation of MCFA is preserved in obesity. Hepatocytes isolated from the Zucker rat (176) demonstrated a reduction of fatty acid oxidation, whose importance varied according to the length of the fatty chain. Compared to the lean controls, the conversion of CO_2 in the obese was diminished by 71% using $C_{16:0}$ compared to only 56% after $C_{8:0}$.

One of the main properties of MCT is their ketogenic character (49, 55, 68, 147, 151) (Fig. 3). Indeed, part of the acetyl-CoA massively produced during MCFA oxidation (177) is directed towards ketone body production. A single oral intake of 45–100 g MCT given alone to healthy subjects increases the ketone body concentration in blood up to 700 µmol/L within 1–2 h, 2 to 4-times higher than those observed after a LCT meal (9, 47, 52, 62) (plasma concentrations: fed healthy subjects, 150 µmol/L; 48 h fast, 2500; untreated diabetes, up to 10,000). With the incorporation of MCT in a well-balanced regimen, the following values have been obtained: 100–500 µmol/L in healthy subjects (82); 370–750 µmol/L in obese women on a low energy diet (16, 63). The level of ketonemia is directly correlated with the MCT supply (50). In controlled diabetics, a 100-g MCT-rich balanced meal causes a rise in plasma ketone body values up to 1000 µmol/L (77), suggesting that the oil is not contraindicated in this morbid condition and that ketonuria (50) and the energy-related losses represent only a few percent of intake. It is worth keeping in mind that ketone bodies fulfill an important physiological role as energy-yielding substrates in extrahepatic tissues (178).

It has been known since the 1930s (179) that the oral administration of MCFA leads to urinary elimination of C_6, C_8, and C_{10} dicarboxylic acids. The same situation occurs in MCT-fed animals or patients (180, 181), with elimination rates of dicarboxylic acids proportional to the lipid charge. As the same end-products are detected

in Reye's syndrome (182) and several inherited disorders characterized by acyl-CoA dehydrogenase deficiencies (183), the severe disturbances accompanying these lethal conditions have thrown some discredit on the use of MCT.

Dicarboxylic acids are obtained by ϖ-oxidation converting the terminal methyl group of fatty acids. This natural metabolic pathway, usually maintained at minimal thresholds, is enhanced in many situations where β-oxidation is either accelerated or overwhelmed, deficient, or blocked. Whatever their chain length or degree of unsaturation, all fatty acids are capable of being ϖ-oxidized, but $C_{8:0}$ to $C_{11:0}$ are more prone to undergo this pathway. The dicarboxylic acids produced are either discharged into the blood or β-oxidized in the liver. The converting process takes place in mitochondria up to succinyl-CoA, or in peroxisomes up to 6–10 carbon diacids, which are then released in the bloodstream to undergo urinary excretion (184). Under usual dietary conditions, the urinary concentrations of these ϖ-derivatives are low (2–15, 1–9, and 1–7 μg/mg creatinine released as adipic, suberic, and sebacic acids in healthy children respectively). They manifest a sharp elevation (58, 116, and 410 μg/mg, respectively) 4 h after the intake of 25 g MCT by a healthy adult (180).

At the concentrations usually met, the dicarboxylic acids show no evident toxic, mutagenic, or teratogenic signs and are even proposed as alternate fuel substrates in parenteral nutrition (185). However, in isolated rat liver mitochondria, ATP production is decreased by medium-chain (186) and even more by long-chain dicarboxylic acids (182). An inventory of the main clinical risks of elevated and/or prolonged administration of MCT has been drawn up (7). Although the processes releasing ϖ-oxidative compounds may vary considerably according to age and circumstances, it is unlikely that this pathway plays any significant role (187) when MCT are ingested by a healthy adult in moderate proportions and in a mixed diet. Indeed, the energy loss due to urinary dicarboxylic acids is small for it does not exceed 2–3% of the amount administered (188, 189).

OVERALL REGULATION

Liver has both high fatty acid synthetic and oxidative capacities that are modulated according to physiopathological conditions and specific body requirements (190). These regulatory mechanisms are basically governed by two key steps working in competitive antagonism. The first step is carnitine palmitoyltransferase, localized on the mitochondrial outer membrane, controlling the conversion of acyl-CoA into acyl-carnitine and, therefore, the rate of mitochondrial fatty acid oxidation. The second is malonyl-CoA, involved in the de novo fatty acid synthesis. At physiological concentrations, this substrate inhibits the production of acyl-CoA and the subsequent penetration and oxidation of fatty acids within the mitochondria (191). As malonyl-CoA inhibits carnitine palmitoyltransferase, high rates of fatty acid synthesis result in low rates of fatty acid oxidation, and vice versa. Due to their relative carnitine-independence, MCFA escape the regulatory steps controlling LCFA. Once in the mitochondrial matrix, β-oxidation is the almost exclusive fate of all fatty acids, whatever the chain length (192). This explains why the oxidation of MCFA is poorly affected by the nutritional or hormonal status of the body (192, 193) contrary to LCFA: carbohydrates reduce the production of CO_2 from $C_{16:0}$ much more than from $C_{8:0}$ (174, 194).

Although carbohydrates do not substantially depress MCFA oxidation rates, they significantly diminish the production of ketone bodies from these fatty acids (49, 193). This concerns another regulating enzyme, 3-hydroxy-3-methylglutaryl-CoA synthetase, the key enzyme of ketogenesis (190). The production of 3-hydroxy-3-methylglutaryl-CoA, and consequently of ketone bodies, is stimulated by acetyl-CoA and inhibited by succinyl-CoA. The anti-ketogenic activity of glucose can thus be explained by the intervention of succinyl-CoA, but perhaps also by the supply of oxaloacetate (195, 196), which is the acceptor of acetyl-CoA in the tricarboxylic cycle.

Taken together, these data imply that MCT are oxidized, even when incorporated in a mixed meal, but ketone body production and the subsequent satiety effect are much attenuated. This is typically observed after a long-term regimen during which the MCT-induced hyperketonemia progressively manifests a lowering trend (45). The dampening effect could result either from peripheral adaptive utilization of ketone bodies (197) or from a greater MCFA incorporation into the hepatic lipids (147), or from both. An MCT supply thus creates a novel situation in the liver: β-oxidation is accelerated, at the same time as the production of malonyl-CoA and subsequent de novo fatty acid synthesis are enhanced (147), though incompatibility between these two routes is classically affirmed. Moreover, MCT display slight tendencies to elevate insulin levels (57) and to promote lipogenesis as a result of an increased insulin/glucagon balance (190). Prolonged MCT-feeding causes adaptive physiological and/or enzymatic changes (45, 154) that progressively favor lipogenic pathways at the relative expense of oxidative processes.

In the adipose tissue, LPL plays a crucial role in the storage of fatty acid (161). The enzyme is unlikely to intervene after MCT-intake because MCFA are only modestly transported by chylomicrons. In contrast, the enzyme is activated after fatty meals in obesity, but also

in most conditions characterized by hypertriglyceridemia and/or hyperinsulinemia (160). The net balance between these opposite influences remains unclear. However, an inhibition of the enzyme activity has been observed in Zucker rat adipose tissue during long-term MCT feeding and reduced energy intake (59).

Some overzealous proponents of MCT claim that the rapid endogenous oxidation of dietary MCFA triggers enhancing effects on LCFA catabolism. To attain such an objective, MCT would have to concomitantly stimulate lipolysis in adipose tissue and oxidation of the released fatty acids. The first step looks unlikely as it is catalyzed by the hormone-sensitive lipase whose activity is strongly inhibited by insulin (198), known to be set in motion by MCT-intake (see Energy Intake section). The second step is only modestly operative in the adipose tissue and mainly confined to the liver. In vitro studies showed that MCFA are slightly more rapidly oxidized by adipocytes than LCFA (132, 141, 199), but the latter fatty acids demonstrate reduced oxidation rates in the presence of MCFA (199). This observation has been confirmed by in vivo studies in suckling rats (130).

ENERGY BALANCE

Dietary intake is accompanied by increased oxygen consumption and energy expenditure. Oxygen consumption during MCT oxidation is augmented compared to LCT, (52, 162), whereas the respiratory quotient (RQ) is identical (61) or slightly more elevated (63) (Table 1). Replacement of LCT with MCT induces an increase of the postprandial RQ in lean but not in obese subjects (200). The evolutionary pattern of the RQ during the 9 h after a fat-supplemented breakfast depends on the nature of the ingested lipids (20). Compared to LCT, the MCT-induced RQ is lower during the first 4–4.5 h, but higher during the last hours of the experiment. These data suggest that MCT allow an initial sparing of some glycogen, undergoing overoxidation during the second half of the experiment.

Exogenous food supply causes a transient increase of energy expenditure, namely the thermic effect of food (TEF). According to some workers, MCT and LCT entail similar TEF (20, 61, 201), whereas others have found that MCT cause a higher effect than LCT (52, 162, 202, 203). Hill et al. (170) unequivocally demonstrated that the TEF curve of healthy volunteers was delayed and did not rejoin the baseline value 6 h after a normal meal containing 40% energy as MCT, in contrast to the response obtained after the intake of LCT. Afterwards, the same volunteers were given a hypercaloric regimen (150% of estimated energy requirements) during 5 days. On the first day, the MCT-induced TEF amounted to 8% of a 1,000 kcal meal and increased to 12% at the end of this 5-day survey. TEF was significantly lower, starting at 5.8% and remaining unchanged at the end of a comparable LCT dietary protocol. An excess dietary MCT thus causes an higher TEF than does excess LCT. However, the increase due to MCT, alone or in a mixed meal, versus LCT is equivalent in lean and in obese subjects (200).

Several hypotheses may be propounded to explain the increased TEF: occurrence of specific regulatory thermogenesis that depend on peroxisomal β-oxidation in brown adipose tissue (203); partial uncoupling of oxidative phosphorylation (202); retroconversion of some ATP molecules produced during the accelerated oxidation of MCFA into ADP, aiming to restore a normal ATP/ADP ratio (204); specific energetic processes within the liver generated either by the production of ketone bodies (43, 45) or by means of "redox cycling" (205) or hepatic de novo synthesis of LCFA (82, 170). In the present state of knowledge, the last two or three proposals may be held as the most likely mechanisms.

Summing up, MCT provide less available energy owing to their lower energy density (see Energy Intake section) and to their higher energy expenditure via thermogenic processes.

BODY WEIGHT AND BODY FAT

Animal studies

According to classical views, the consumption of MCT-based regimens causes a reduction in final body weight when compared to LCT-regimens. This result is grounded on many experiments performed mainly on rats, and notably on Zucker obese rats (59, 60), but also on other animal models (75, 76, 206, 207) (**Fig. 5**). The decrease in body weight results mainly from the shrinking of fat depots (3, 12, 44, 56, 58, 97, 137, 139, 154, 162, 208), leading to the reduction in the relative content of lipids in the whole body (14, 45, 59, 60, 97, 137, 207, 209). The number of adipocytes appears independent of the nature of the alimentary lipids (12, 59, 61, 99, 162, 202, 208), whereas their mean size is smaller in MCT- versus LCT-fed rats. Some workers defend the view of a relative gain in protein (45, 207) and/or in water compartments (59, 60, 207), while others support the concept that the whole body N pool remains unmodified (12, 14, 60, 97, 153, 154). In any case, the N retention (14, 45, 60, 154, 207) and the fractional synthetic rate of protein in the body (14) yield superimposable data for both LCT and MCT experiments. In obese women on a low-calorie diet, the N balance is either identical (16) or "somewhat higher" (63) with MCT than with LCT.

In experimental conditions aimed at slimming effects,

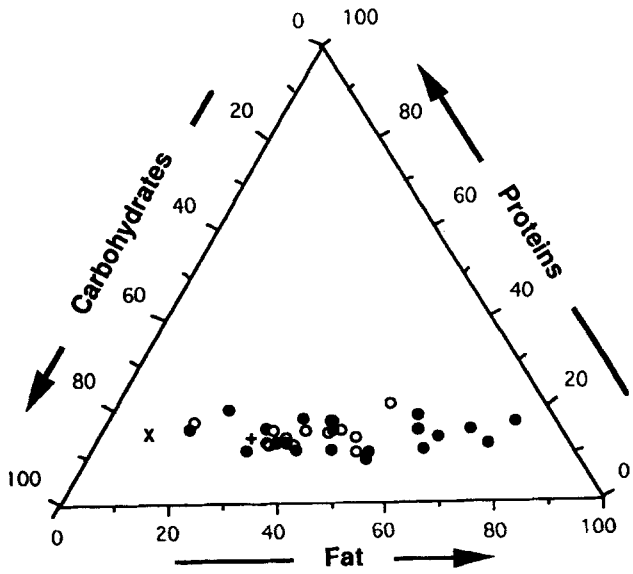

Fig. 5. Effect of MCT (versus LCT) on final body weight of laboratory animals (mostly rats). Each point, determined by the intersection of three coordinates indicating the proportion (% kcal) of macronutrient classes, represents the result of one study. Data are derived from following references: (3, 12, 14, 18, 26, 44, 45, 55–61, 73, 74, 97, 135–137, 142, 146, 152, 154, 162, 164, 165, 206, 208, 209, 211, 220). Black circles: the final body weight of MCT-fed animals is lower than that recorded in LCT-fed controls; open circles: the final body weight is identical in both MCT and LCT experiments; (X): dietary standards for laboratory rodents (fat, 9.5%; protein, 14.70%; carbohydrates, 75.8%) (221); (+): recommended dietary allowances for human beings (fat, 30%; protein, 15%, carbohydrates, 55%) (222). This figure shows that final body weight is significantly reduced (versus LCT) by all regimens providing at least 50% lipid energy as MCT.

a lower energy intake is not necessarily a "contributory" factor. A direct relationship between energy restriction and reduction in body weight gain has been established in some surveys (55, 56, 74–76, 164) (Figs. 1 and 5). In about two-thirds of the studies, the body weight-reducing property of MCT has been obtained in spite of identical energy consumption, in ad libitum and in pair-fed experiments. This explains why several investigators (3, 18, 56, 60, 74, 137, 139, 165, 209, 210) point to a diminished energy efficiency of MCT, implying that relatively more MCT are required to reach the same body weight gain as obtained after LCT. Utilization of pair-feeding techniques allowing us to compensate for the difference in energy intakes has provided support for a lower efficiency of MCT (14, 59, 208). It is likely that the reduced efficiency of MCT correlates with the increase in TEF (see Energy Balance section).

In about one-third of the surveys (Fig. 5) no difference in the evolutionary patterns of body weight (26, 57, 61, 73, 134, 146, 153, 164, 206, 211, 212), body fat (61, 136), and energy efficiency (55, 61, 97, 135, 136, 207) was recorded between MCT and LCT regimens. How can these discrepant views be reconciled? Certainly, the selection of a particular animal model may play a role, and it is plausible that the chicken's requirements are different from those of the rat (213). Young animals are characterized by an overall immaturity likely to affect more deeply the digestion, absorption, and transport of LCT than MCT (213). Therefore, MCT data recorded in such a model can hardly be extrapolated to mature animals. In liver slices, it has been shown (214) that the ratio between CO_2 and ketone body production from octanoate is strikingly different in growing versus adult rats. The dissipation of food as heat is more efficient in younger animals whereas storage as fat is more marked in older animals (215). According to Chanez et al. (154), the duration of the regimen is of crucial importance, with a marked MCT-induced slimming effect in the short term, but prone to vanish in the long term. Chanez's observation, however, is not supported by the experimental data usually found in the current literature.

Let us now consider the composition of the diet. A careful follow-up of the experimental surveys indicates that the nature of proteins (usually casein) and of carbohydrates (glucose, sucrose, starch, or maltodextrins) is unable to explain the observed discrepancies. Although the type of LCT (mostly corn, but also olive, soybean, sunflower, lard, fish oils) has an undisputed influence on the body weight gain (61, 73, 97), it cannot account for the disparity of the results obtained after MCT or LCT. Furthermore, the hypothesis of a deficit in EFA is not sustainable. Such an artifactual deprivation likely occurred in only one experiment (99), unexpectedly resulting in increased body weight gain of MCT-fed rats. The amount of fat in the regimen is of utmost importance. Although Fig. 5 indicated that slimming trends are sometimes recorded after low MCT supply, most experiments put emphasis on the fact that the threshold of 50% energy must be reached to obtain a reproducible body weight-reducing effect (56, 142). When this critical margin is overshot, increasing the MCT/LCT ratio within isocaloric regimens leads to a significant slackening of the body weight gain (56, 76, 165, 207). On the other hand, increasing both fat supply and total energy intake augments the body weight of LCT-fed rats more than that of MCT-fed rats (3, 18, 56, 75, 152, 206). The gap between the two body weight curves is even more pronounced as some studies indicate that MCT regimens stabilize body weight (18, 26, 56, 152, 206).

Lastly, some recent data lend credence to the idea that the relative proportions of $C_{8:0}$ and $C_{10:0}$ within the MCT molecule could influence its biological fate and therefore its potential applications. MCT exhibit quite a large spectrum of fatty acid composition according to the manufacturers (216). Indeed, we have emphasized minor differences in the behavior of each MCFA through-

out this review: versus decanoate, octanoate has among other properties a higher oxidation rate, a lower energy supply, and a diminished ability to form complex lipids. It may be that these minor metabolic differences could, in the long run, exert functional consequences on the whole body economy. As early as 1970, Aurousseau, de Groot, and Vermorel (139), followed by several other groups (39, 40, 50, 75, 136, 137, 152, 213), tested trioctanoate rather than usual MCT to reach maximal efficiency.

Clinical assays

One of the most enthusiastic clinical surveys, performed by Kaunitz et al. in 1958 (3), reported a body weight loss up to 13 kg in 20 obese patients after a 2-month MCT regimen. Twenty years later, the same author (11) drew back by stating that a low energy diet (1, 200 kcal) providing 50 g MCT was more effective in reducing body weight than a butter–corn oil mixture, but the "difference was not dramatic".

Twenty-four obese women experienced severe fasting during 5 consecutive days before undergoing two different hypocaloric diets for 3 weeks (63): 12 were on a 550 kcal regimen providing 50 g protein and 30 g MCT, and the others received a 500-kcal regimen with 60 g protein and 10 g LCT as whipped cream. At the end of the experiment, body weight losses were identical in both groups. Another clinical survey was set up by Yost and Eckel (16) who enrolled 16 obese women in two different hypocaloric regimens (800 kcal and 30% energy as fat supply) for 4 or 12 weeks. The first regimen comprised only LCT, whereas the second consisted of 6% LCT and 24% MCT. Here too, the recorded body weight losses were comparable with both lipids. Finally, Hill et al. (82, 170) investigated 10 non-obese volunteers who were given a regimen providing 150% of the recommended dietary allowances for 6 days. Lipids were ingested as 40% LCT or 40% MCT in a randomized crossover design. No significant change in body weight was recorded at the end of either diet protocol.

CONCLUSIONS AND PERSPECTIVES

We have recalled many specific physico-chemical and metabolic characteristics of MCT/MCFA. Some of these peculiarities, high stability, refractoriness to peroxidation, pleasant oily flavor shared in common with most dietary lipids, plead on behalf of the usefulness of MCT in human nutrition. Moreover, these lipids have unique properties that meet increased energy requirements of stressed patients and promote their nutritional rehabilitation and tissue repair. Therefore, it is all the more surprising to point out that the same substrate is also advocated as an efficient tool aiming at reducing body weight. Indeed, MCT/MCFA are endowed in that prospect with potentially helpful properties versus LCT/LCFA: increasing feeling of satiety, slightly reduced energy density, rapid entero-portal transportation and intrahepatic oxidation explaining their poor incorporation (as MCFA) into complex lipids, and wasting of part of the released energy. Summing up, Senior (18) and Spielmann et al. (217) contend that MCFA function as energy-yielding substrates devoid of any structural or physiological role. Other aspects argue, nevertheless, against the use of MCT as body weight-reducing substrates: higher energy recovery from intestinal absorption rates, through the mediation of ketone bodies, stimulation of insulin secretion and related anabolic processes such as entry of glucose into adipocytes and enhancement of lipogenesis, and inhibition of the hormone-sensitive lipase, resulting in the preservation of body fat stores.

Referring now to experimental data, many investigators using animal models found that MCT are capable of exerting slight weight-reducing effects. These results, however, are far from reaching overall consensus. The balance between body weight-reducing and body weight-increasing effects seem to vary widely, indicating that the conditions allowing the scale to shift from one side to the other need to be more fully substantiated. Nevertheless, the debate remains partly open in the light of recent data (see Body Weight and Body Fat section) suggesting that trioctanoate, endowed with the highest MCT potential, could be more efficient in lowering body weight. In human studies, the promising slimming potential of MCT is poorly documented in the current literature and convincing clinical studies in support of the concept are rare and rather disappointing. For a wide variety of reasons, the positive and negative impacts of MCT on body weight vary among experiments, though ultimately always rather small.

Experimental studies using dietary manipulation with MCT as sole lipid source are quite easy to perform in animals, but cannot be extrapolated to human subjects. The difficulty in doing such clinical surveys is not linked to the EFA optimal requirements, easily covered by supplementation, but to the unpleasant consequences of monotony. Theoretically, this obstacle might be circumvented by incorporating MCT within a variety of hypocaloric regimens or within meal substitutes. However, the efficacy of MCT in reducing body weight is expected to diminish in proportion to its dilution in mixed regimens. The threshold of 50% MCT requisite to attain clinical results implies poor compliance with the proposed regimen. In other words, and even if some body weight-reducing effects of MCT might benefit from further development, such a long-term regimen is

questionable in human subjects. Hence, not a single word is provided about the dietetic role of MCT in authoritative position papers devoted to the treatment of obesity (1, 218, 219).

The graphical contribution performed by Mr. Thierry Zorn is gratefully acknowledged.

Manuscript received 21 September 1995 and in revised form 5 January 1996.

REFERENCES

1. Atkinson, R. L. 1992. Treatment of obesity. *Nutr. Rev.* **50:** 338–345.
2. Weitzel, G. 1950. Ernährungstherapie mit Fettsäuren. *Fette-Seifen* **11:** 670–675.
3. Kaunitz, H., C. A. Slanetz, R. E. Johnson, V. K. Babayan, and G. Barsky. 1958. Relation of saturated, medium- and long-chain triglycerides to growth, appetite, thirst and weight maintenance requirements. *J. Nutr.* **64:** 513–524.
4. Bach, A. C., and V. K. Babayan. 1982. Medium-chain triglycerides: an update. *Am. J. Clin. Nutr.* **36:** 950–962.
5. Megremis, C. J. 1991. Medium chain triglycerides: a non-conventional fat. *Food Technol.* **45:** 108–114.
6. Timmermann, F. 1993. Medium chain triglycerides. The unconventional oil. *Int. Food Ingredients.* **3:** 11–18.
7. Ingenbleek, Y. 1989. Les triglycérides à chaînes moyennes en nutrition clinique. *Nutr. Clin. Métabol.* **3:** 3–15.
8. Bach, A. C., A. Frey, and O. Lutz. 1989. Clinical and experimental effects of medium-chain-triglyceride-based fat emulsions. A review. *Clin. Nutr.* **8:** 223–235.
9. Schön, H., I. Lippach, and W. Gelpke. 1959. Stoffwechseluntersuchungen mit einem Mischglycerid der Fettsäuren mittlerer Kettenlänge. II. Untersuchungen über die Veränderungen des Ketonkörpergehaltes von Blut und Urin nach Zufuhr des Mischglycerides. *Gastroenterologia.* **91:** 199–213.
10. Senior, J. R. 1968. Introductory remarks by the chairman. *In* Medium Chain Triglycerides. J. R. Senior, editor. University of Pennsylvania Press, Philadelphia. 3–7.
11. Kaunitz, H. 1978. Clinical uses of medium-chain triglycerides. *Drug. Ther.* **16:** 91–99.
12. Geliebter, A., N. Torbay, E. F. Bracco, S. A. Hashim, and T. B. Van Itallie. 1983. Overfeeding with medium-chain triglyceride diet results in diminished deposition of fat. *Am. J. Clin. Nutr.* **37:** 1–4.
13. Geliebter, A., E. F. Bracco, T. B. Van Itallie, and S. A. Hashim. 1984. Medium-chain triglyceride diet and obesity. *Int. J. Obes.* **8:** 191–192.
14. Ling, P. R., K. J. Hamawy, L. L. Moldawer, N. Istfan, B. R. Bistrian, and G. L. Blackburn. 1986. Evaluation of the protein quality of diets containing medium- and long-chain triglyceride in healthy rats. *J. Nutr.* **116:** 343–349.
15. Babayan, V. K. 1989. Medium chain triglycerides. *J. Am. Oil Chem. Soc.* **66:** 73–86.
16. Yost, T. J., and R. H. Eckel. 1989. Hypocaloric feeding in obese women: metabolic effects of medium-chain triglyceride substitution. *Am. J. Clin. Nutr.* **49:** 326–330.
17. Hamosh, M., M. L. Spear, J. Bitman, N. R. Mehta, D. L. Wood, and P. Hamosh. 1991. Medium chain triglycerides: advantages and possible drawbacks. *In* Inborn Errors of Metabolism. J. Schaub, F. Van Hoof, and H. L. Vis, editors. Vevey Raven Press, New York. 81–92.
18. Senior, J. R. 1968. Summary panel on role of medium chain triglycerides in human disease states and possible future applications. *In* Medium Chain Triglycerides. J. R. Senior, editor. University Pennsylvania Press, Philadelphia. 247–260.
19. Zulak, G. 1991. MCT oil: the fact about fatless fat. *Flex.* 125–161.
20. Flatt, J. P., E. Ravussin, K. J. Acheson, and E. Jéquier. 1985. Effects of dietary fat on postprandial substrate oxidation and on carbohydrate and fat balances. *J. Clin. Invest.* **76:** 1019–1024.
21. Lissner, L., and B. L. Heitmann. 1995. Dietary fat and obesity: evidence from epidemiology. *Eur. J. Clin. Nutr.* **49:** 79–90.
22. Flatt, J. P. 1987. Dietary fat, carbohydrate balance, and weight maintenance: effects of exercise. *Am. J. Clin. Nutr.* **45:** 296–306.
23. Livesey, G., and M. Elia. 1988. Estimation of energy expenditure, net carbohydrate utilization, and net fat oxidation and synthesis by indirect calorimetry: evaluation of errors with special reference to the detailed composition of fuels. *Am. J. Clin. Nutr.* **47:** 608–628.
24. Bracco, U. 1976. Medium-chain triglycerides: characteristics and uses. *In* Lipids: Technology. R. Paoletti, G. Jacini, and R. Porcellati, editors. Raven Press, New York. 401–409.
25. Hamosh, M. 1984. Lingual lipase. *In* Lipases. B. Borgström, and H. L. Brockman, editors. Elsevier, Amsterdam. 49–81.
26. Edens, N. K., and M. I. Friedman. 1984. Response of normal and diabetic rats to increasing dietary medium-chain triglyceride content. *J. Nutr.* **114:** 565–573.
27. Maggio, C. A., and H. S. Koopmans. 1982. Food intake after intragastric meals of short-, medium-, or long-chain triglyceride. *Physiol. Behav.* **28:** 921–926.
28. Greenberger, N. J., and T. G. Skillman. 1969. Medium-chain triglycerides. Physiologic considerations and clinical implications. *N. Engl. J. Med.* **280:** 1045–1058.
29. Ruppin, D. C., and W. R. J. Middleton. 1980. Clinical use of medium chain triglycerides. *Drugs.* **20:** 216–224.
30. Rolls, B. J., N. Gnizak, A. Summerfelt, and L. J. Laster. 1988. Food intake in dieters and nondieters after a liquid meal containing medium-chain triglycerides. *Am. J. Clin. Nutr.* **48:** 66–71.
31. Harkins, R. W., J. B. Longenecker, and H. P. Sarret. 1964. The effect of the type and level of dietary fat on gastric retention in rats. *Gastroenterology.* **47:** 65–71.
32. Hunt, J. N., and M. T. Knox. 1968. A relation between the chain length of fatty acids and the slowing of gastric emptying. *J. Physiol. (London).* **194:** 327–336.
33. Hopman, W. P. M., J. B. M. J. Jansen, G. Rosenbusch, and C. B. H. W. Lamers. 1984. Effect of equimolar amounts of long-chain triglycerides and medium-chain triglycerides on plasma cholecystokinin and gallbladder contraction. *Am. J. Clin. Nutr.* **39:** 356–359.
34. Pirk, F., and I. Skala. 1970. Motility of the digestive tract after administration of medium chain triglycerides (MCT) as compared with long chain triglycerides (LCT). *Digestion.* **3:** 73–80.
35. Maggio, C. A., and H. S. Koopmans. 1987. Satiety effects of intragastric meals containing triglycerides with different chain lengths. *Am. J. Physiol.* **252:** R1106–R1113.
36. Isaacs, P. E. T., S. Ladas, I. C. Forgacs, R. H. Dowling, S. V. Ellam, T. E. Adrian, and S. R. Bloom. 1987. Comparison of effects of ingested medium- and long-chain

triglyceride on gallbladder volume and release of cholecystokinin and other gut peptides. *Dig. Dis. Sci.* **32:** 481–486.
37. Douglas, B. R., J. B. M. J. Jansen, A. J. L. de Jong, and C. B. H. W. Lamers. 1990. Effect of various triglycerides on plasma cholecystokinin levels in rats. *J. Nutr.* **120:** 686–690.
38. Mabayo, R. T., M. Furuse, S. I. Yang, and J. I. Okumura. 1992. Medium-chain triacylglycerols enhance release of cholecystokinin in chicks. *J. Nutr.* **122:** 1702–1705.
39. Furuse, M., Y. H. Choi, R. T. Mabayo, and J. I. Okumura. 1992. Feeding behavior in rats fed diets containing medium chain triglyceride. *Physiol. Behav.* **52:** 815–817.
40. Furuse, M., R. T. Mabayo, Y. H. Choi, D. M. Denbow, and J. Okumura. 1993. Feeding behavior in chickens given diets containing medium chain triglyceride. *Br. Poultry Sci.* **34:** 211–217.
41. Van Itallie, T. B., and H. R. Kissileff. 1985. Physiology of energy intake: an inventory control model. *Am. J. Clin. Nutr.* **42:** 914–923.
42. Davis, J. D., D. Wirtshafter, K. E. Asin, and D. Brief. 1981. Sustained intracerebroventricular infusion of brain fuels reduces body weight and food intake in rats. *Science.* **212:** 81–83.
43. McCarty, M. F. 1994. Promotion of hepatic lipid oxidation and gluconeogenesis as a strategy for appetite control. *Med. Hypotheses.* **42:** 215–225.
44. Lavau, M. M., V. Fornari, and S. A. Hashim. 1978. Ketone metabolism in brain slices from rats with diet induced hyperketonemia. *J. Nutr.* **108:** 621–629.
45. Crozier, G., B. Bois-Joyeux, M. Chanez, J. Girard, and J. Peret. 1987. Metabolic effects induced by long-term feeding of medium-chain triglycerides in the rat. *Metabolism.* **36:** 807–814.
46. Flatt, J. P. 1988. Importance of nutrient balance in body weight regulation. *Diabetes Metab. Rev.* **4:** 571–581.
47. Pi-Sunyer, F. X., S. A. Hashim, and T. B. Van Itallie. 1969. Insulin and ketone responses to ingestion of medium and long-chain triglycerides in man. *Diabetes.* **18:** 96–100.
48. Bach, A. 1974. Hypoglykämie und Hyperinsulinismus nach mittelkettigen Triglyceriden. *Z. Ernährungswiss.* **Suppl. 17:** 27–35.
49. Yeh, Y. Y., and P. Zee. 1976. Relation of ketosis to metabolic changes induced by acute medium-chain triglyceride feeding in rats. *J. Nutr.* **106:** 58–67.
50. Nakamura, T., D. Yoshihara, T. Ohmori, M. Yanai, and Y. Takeshita. 1994. Effects of diet high in medium-chain triglyceride on plasma ketone, glucose, and insulin concentrations in enterectomized and normal rats. *J. Nutr. Sci. Vitaminol.* **40:** 147–159.
51. Bach, A., A. Weryha, and H. Schirardin. 1979. Influence of oral MCT or LCT load on glycemia in Wistar and Zucker rats and guinea pigs. *Ann. Biol. Anim. Biochim. Biophys.* **19:** 625–635.
52. Seaton, T. B., S. L. Welle, M. K. Warenko, and R. G. Campbell. 1986. Thermic effect of medium-chain and long-chain triglycerides in man. *Am. J. Clin. Nutr.* **44:** 630–634.
53. Opara, E. C., M. Garfinkel, V. S. Hubbard, W. M. Burch, and O. E. Akwari. 1994. Effect of fatty acids on insulin release: role of chain length and degree of unsaturation. *Am. J. Physiol.* **266:** E635–E639.
54. Madison, L. L., D. Mebane, R. H. Unger, and A. Lochner. 1964. The hypoglycemic action of ketones. II. Evidence for a stimulatory feedback of ketones on the pancreatic beta cells. *J. Clin. Invest.* **43:** 408–415.
55. Wiley, J. H., and G. A. Leveille. 1973. Metabolic consequences of dietary medium-chain triglycerides in the rat. *J. Nutr.* **103:** 829–835.
56. Bray, G. A., M. Lee, and T. L. Bray. 1980. Weight gain of rats fed medium-chain triglycerides is less than rats fed long-chain triglycerides. *Int. J. Obes.* **4:** 27–32.
57. Takase, S., and N. Hosoya. 1987. Possible role of insulin status in the increased lipogenic enzyme activity by dietary medium-chain triglyceride in rat liver. *J. Nutr. Sci. Vitaminol.* **33:** 177–184.
58. Lavau, M. M., and S. A. Hashim. 1978. Effect of medium chain triglyceride on lipogenesis and body fat in the rat. *J. Nutr.* **108:** 613–620.
59. Turkenkopf, I. J., C. A. Maggio, and M. R. C. Greenwood. 1982. Effect of high fat weanling diets containing either medium-chain triglycerides or long-chain triglycerides on the development of obesity in the Zucker rat. *J. Nutr.* **112:** 1254–1263.
60. Bach, A. C., B. Bois-Joyeux, M. Chanez, B. Delhomme, H. Schirardin, and J. Peret. 1984. Metabolic effects of medium- or long-chain triglycerides and high-protein, carbohydrate-free diets in Zucker rats. *Metabolism.* **33:** 951–958.
61. Hill, J. O., J. C. Peters, D. Lin, F. Yakubu, H. Greene, and L. Swift. 1993. Lipid accumulation and body fat distribution is influenced by type of dietary fat fed to rats. *Int. J. Obes.* **17:** 223–236.
62. Tantibhedhyangkul, P., S. A. Hashim, and T. B. Van Ittalie. 1967. Effects of ingestion of long-chain and medium-chain triglycerides on glucose tolerance in man. *Diabetes.* **16:** 796–799.
63. Rath, R., I. Skala, and E. Rathova. 1972. Metabolic aspects of the use of medium chain triglycerides in the treatment of obesity. *Z. Ernährungswiss.* **13:** 116–124.
64. Wilson, D. E., I. F. Chan, K. B. Stevenson, S. C. Horton, and C. Schipke. 1983. Eucaloric substitution of medium chain triglycerides for dietary long chain fatty acids in acquired total lipodystrophy: effects on hyperlipoproteinemia and endogenous insulin resistance. *J. Clin. Endocrinol. Metab.* **57:** 517–523.
65. Eckel, R. H., A. S. Hanson, A. Y. Chen, J. N. Berman, T. J. Yost, and E. P. Brass. 1992. Dietary substitution of medium-chain triglycerides improves insulin-mediated glucose metabolism in NIDDM subjects. *Diabetes.* **41:** 641–647.
66. Mebane, D., and L. L. Madison. 1964. Hypoglycemic action of ketones. I. Effects of ketones on hepatic glucose output and peripheral glucose utilization. *J. Lab. Clin. Med.* **63:** 177–192.
67. Sanbar, S. S., G. Hetenyi, N. Forbath, and J. R. Evans. 1965. Effects of infusion of octanoate on glucose concentration in plasma and the rates of glucose production and utilization in dogs. *Metabolism.* **14:** 1311–1323.
68. Guy, D. G., and R. J. Tuley. 1981. Effect of diets high in carbohydrate, soy oil, medium-chain triglycerides or tripelargonin on blood and liver lipid and glucose intermediates in meal-eating rats. *J. Nutr.* **111:** 1437–1445.
69. Randle, P. J., A. L. Kerberg, and J. Espinal. 1988. Mechanisms decreasing glucose oxidation in diabetes and starvation: role of lipid fuels and hormones. *Diabetes Metab. Rev.* **4:** 623–638.
70. Grossman, S. P. 1975. Role of the hypothalamus in the regulation of food and water intake. *Psychol. Rev.* **82:** 200–224.
71. Friedman, M. I., N. K. Edens, and I. Ramirez. 1983.

Differential effects of medium- and long-chain triglycerides on food intake of normal and diabetic rats. *Physiol. Behav.* **31:** 851–855.
72. Satabin, P., E. Auclair, E. Servan, C. L. Larue Achagiotis, and C. Y. Guezennec. 1991. Influence of glucose, medium- and long-chain triglyceride gastric loads and forced exercise on food intake and body weight in rats. *Physiol. Behav.* **50:** 147–150.
73. Takase, S., and N. Hosoya. 1986. Effect of dietary medium chain triglyceride on lipogenic enzyme activity in rat liver. *J. Nutr. Sci. Vitaminol.* **32:** 219–227.
74. Webb, D. R., J. C. Peters, R. J. Jandacek, and N. E. Fortier. 1991. Caprenin. 2. Short-term safety and metabolism in rats and hamsters. *J. Am. Coll. Toxicol.* **10:** 341–356.
75. Furuse, M., R. T. Mabayo, K. Kita, and J. Okumura. 1992. Effect of dietary medium chain triglyceride on protein and energy utilisation in growing chicks. *Br. Poultry Sci.* **33:** 49–57.
76. Mabayo, R. T., M. Furuse, A. Murai, and J. I. Okumura. 1994. Interactions between medium-chain and long-chain triacylglycerols in lipid and energy metabolism in growing chicks. *Lipids.* **29:** 139–144.
77. Bergen, S. S., S. A. Hashim, and T. B. Van Itallie. 1966. Hyperketonemia induced in man by medium chain triglyceride. *Diabetes.* **15:** 723–725.
78. Sucher, K. P. 1986. Medium chain triglycerides: a review of their enteral use in clinical nutrition. *Nutr. Clin. Pract.* **1:** 146–150.
79. Holt, P. R. 1967. Medium chain triglycerides. A useful adjunct in nutritional therapy. *Gastroenterology.* **53:** 961–966.
80. Linscheer, W. G., A. L. Blum, and R. R. Platt. 1970. Transfer of medium chain fatty acids from blood to spinal fluid in patients with cirrhosis. *Gastroenterology.* **58:** 509–515.
81. Odle, J., N. J. Benevenga, and T. D. Crenshaw. 1991. Utilization of medium-chain triglycerides by neonatal piglets: chain length of even and odd-carbon fatty acids and apparent digestion/absorption and hepatic metabolism. *J. Nutr.* **121:** 605–614.
82. Hill, J. O., J. C. Peters, L. L. Swift, D. Yang, T. Sharp, N. Abumrad, and H. L. Greene. 1990. Changes in blood lipids during six days of overfeeding with medium or long chain triglycerides. *J. Lipid Res.* **31:** 407–416.
83. Linscheer, W. G., J. F. Patterson, E. W. Moore, R. J. Clermont, S. R. Robins, and T. C. Chalmers. 1966. Medium and long chain fat absorption in patients with cirrhosis. *J. Clin. Invest.* **45:** 1317–1325.
84. Guillot, E., P. Vaugelade, P. Lemarchal, and A. Rérat. 1993. Intestinal absorption and liver uptake of medium-chain fatty acids in non-anaesthetized pigs. *Br. J. Nutr.* **69:** 431–442.
85. Odle, J., X. I. Lin, T. M. Wieland, and T. A. T. G. Van Kempen. 1994. Emulsification and fatty acid chain length affect the kinetics of [^{14}C]-medium-chain triacylglycerol utilization by neonatal piglets. *J. Nutr.* **124:** 84–93.
86. Rabinowitz, J. L., J. Staeffen, P. Blanquet, J. D. Vincent, R. Terme, C. Series, and R. M. Myerson. 1978. Sources of serum [^{14}C]octanoate in cirrhosis of the liver and hepatic encephalopathy. *J. Lab. Clin. Med.* **91:** 223–227.
87. Mitkov, D., D. Toreva, A. Krustev, I. Kostadinova, and S. Jumbasova. 1989. On octanoic acid-induced hyperventilation: implications for hepatic encephalopathy and Reye's syndrome. *Res. Exp. Med.* **189:** 347–354.
88. Spector, A. A. 1975. Fatty acid binding to plasma albumin. *J. Lipid Res.* **16:** 165–179.
89. Morgan, M. H., C. H. Bolton, J. S. Morris, and A. E. Read. 1974. Medium chain triglycerides and hepatic encephalopathy. *Gut.* **15:** 180–184.
90. Smith, J., J. Horowitz, J. M. Henderson, and S. Heymsfield. 1982. Enteral hyperalimentation in undernourished patients with cirrhosis and ascites. *Am. J. Clin. Nutr.* **35:** 56–72.
91. Fernando-Warnakulasuriya, G. J. P., J. E. Staggers, S. C. Frost, and M. A. Wells. 1981. Studies on fat digestion, absorption, and transport in the suckling rat. I. Fatty acid composition and concentrations of major lipid components. *J. Lipid Res.* **22:** 668–674.
92. Staggers, J. E., G. J. Fernando-Warnakulasuriya, and M. A. Wells. 1981. Studies on fat digestion, absorption, and transport in the suckling rat. II. Triacylglycerols: molecular species, stereospecific analysis, and specificity of hydrolysis by lingual lipase. *J. Lipid Res.* **22:** 675–679.
93. Hamosh, M., J. Bitman, T. H. Liao, N. R. Mehta, R. J. Buczek, D. L. Wood, L. J. Grylack, and P. Hamosh. 1989. Gastric lipolysis and fat absorption in preterm infants: effects of medium-chain triglyceride or long-chain triglyceride-containing formulas. *Pediatrics.* **83:** 86–92.
94. Greenberger, N. J., J. B. Rodgers, and K. J. Isselbacher. 1966. Absorption of medium and long chain triglycerides: factors influencing their hydrolysis and transport. *J. Clin. Invest.* **45:** 217–227.
95. Borgström, B., and J. S. Patton. 1991. Luminal events in gastrointestinal lipid digestion. *In* Handbook of Physiology. The Gastrointestinal System. S. G. Schultz, editor. American Physiological Society, Bethesda. 475–504.
96. Isselbacher, K. J. 1968. Mechanisms of absorption of long and medium chain triglycerides. *In* Medium Chain Triglycerides. J. R. Senior, editor. University of Pennsylvania Press. 21–34.
97. Harkins, R. W., and H. P. Sarett. 1968. Nutritional evaluation of medium-chain triglycerides in the rat. *J. Am. Oil Chem. Soc.* **45:** 26–30.
98. Roy, C. C., M. Ste-Marie, L. Chartrand, A. Weber, H. Bard, and B. Doray. 1975. Correction of the malabsorption of the preterm infant with a medium-chain triglyceride formula. *J. Pediat.* **86:** 446–450.
99. Lau, H. C., E. Flaim, and S. J. Ritchey. 1979. Body weight and depot fat changes as influenced by exercise and dietary fat sources in adult BHE rats. *J. Nutr.* **109:** 495–500.
100. Jensen, C., N. R. M. Buist, and T. Wilson. 1986. Absorption of individual fatty acids from long chain or medium chain triglycerides in very small infants. *Am. J. Clin. Invest.* **43:** 745–751.
101. Sulkers, E. J., J. B. van Goudoever, C. Leunisse, J. L. D. Wattimena, and P. J. J. Sauer. 1992. Comparison of two preterm formulas with or without addition of medium-chain triglycerides (MCTs). I. Effects on nitrogen and fat balance and body composition changes. *J. Pediat. Gastroenterol. Nutr.* **15:** 34–41.
102. Bloom, B., I. L. Chaikoff, and W. O. Reinhardt. 1951. Intestinal lymph as pathway for transport of absorbed fatty acids of different chain lengths. *Am. J. Physiol.* **166:** 451–455.
103. Tso, P., and J. A. Balint. 1986. Formation and transport of chylomicrons by enterocytes to the lymphatics. *Am. J. Physiol.* **250:** G715–G726.
104. Hashim, S. A. 1968. Studies of medium chain fatty acid transport in portal blood. *In* Medium Chain Triglycerides.

J. R. Senior, editor. University Press, Pennsylvania. 81–90.
105. Malagelada, J. R., F. L. Iber, and W. G. Linscheer. 1974. Origin of fat in chylous ascites of patients with liver cirrhosis. *Gastroenterology.* **67:** 878–886.
106. Wells, M. A. 1985. Fatty acid metabolism and ketone formation in the suckling rat. *Fed. Proc.* **44:** 2365–2368.
107. Jensen, G. L., E. A. Mascioli, L. P. Meyer, S. M. Lopes, S. J. Bell, V. K. Babayan, G. L. Blackburn, and B. R. Bistrian. 1989. Dietary modification of chyle composition in chylothorax. *Gastroenterology.* **97:** 761–765.
108. Swift, L. L., J. O. Hill, J. C. Peters, and H. L. Greene. 1990. Medium-chain fatty acids: evidence for incorporation into chylomicron triglycerides in humans. *Am. J. Clin. Nutr.* **52:** 834–836.
109. Lee, D. S., S. A. Hashim, and T. B. Van Ittalie. 1968. Effect of long chain triglyceride on chylous transport of medium chain fatty acids. *Am. J. Physiol.* **214:** 294–297.
110. Christophe, A., G. Verdonk, M. Mashaly, and P. Sandra. 1982. Fatty acid chain length combinations in ascitic fluid triglycerides containing lymphatic absorbed medium-chain fatty acids. *Lipids.* **17:** 759–761.
111. Ohkubo, Y., S. Mori, Y. Ishikawa, K. Shirai, Y. Saito, and S. Yoshida. 1992. Presence and properties of acyl coenzyme A synthetase for medium-chain fatty acids in rat intestinal mucosa. *Digestion.* **51:** 42–50.
112. Zurier, R. B., R. G. Campbell, S. A. Hashim, and T. B. Van Itallie. 1967. Enrichment of depot fat with odd and even numbered medium chain fatty acids. *Am. J. Physiol.* **212:** 291–294.
113. Rebouche, C. J., D. D. Panagides, and S. E. Nelson. 1990. Role of carnitine in utilization of dietary medium-chain triglycerides by term infants. *Am. J. Clin. Nutr.* **52:** 820–824.
114. Jackson, R. L. 1983. Lipoprotein lipase and hepatic lipase. *In* The Enzymes. P. D. Boyer, editor. Academic Press, London. 141–181.
115. Brindley, D. N., and N. Lawson. 1983. Control of triglyceride synthesis. *In* The Adipocyte and Obesity: Cellular and Molecular Mechanisms. A. Angel, C. H. Hollenberg, and D. A. K. Roncari, editors. Raven Press, New York. 155–164.
116. Robinson, D. S., A. Cryer, and P. Davies. 1975. The role of clearing-factor lipase (lipoprotein lipase) in the transport of plasma triglycerides. *Proc. Nutr. Soc. Engl. Scot.* **34:** 211–215.
117. Richelsen, B., S. B. Pedersen, T. Moller-Pedersen, O. Schmitz, N. Moller, and J. D. Borglum. 1993. Lipoprotein lipase activity in muscle tissue influenced by fatness, fat distribution and insulin in obese females. *Eur. J. Clin. Invest.* **23:** 226–233.
118. Kern, P. A., J. M. Ong, B. Saffari, and J. Carty. 1990. The effects of weight loss on the activity and expression of adipose-tissue lipoprotein lipase in very obese humans. *N. Engl. J. Med.* **322:** 1053–1059.
119. Petit, D., A. Raisonnier, N. Amit, and R. Infante. 1982. Lack of induction of VLDL apoprotein synthesis by medium chain fatty acids in the isolated rat liver. *Ann. Nutr. Métab.* **26:** 279–286.
120. Veerkamp, J. H., T. H. M. S. M. Van Kuppevelt, R. G. H. J. Maatman, and C. F. M. Prinsen. 1993. Structural and functional aspects of cytosolic fatty acid-binding proteins. *Prostaglandins Leukot. Essent. Fatty Acids.* **49:** 887–906.
121. Ockner, R. K., J. A. Manning, R. B. Poppenhausen, and W. K. L. Ho. 1972. A binding protein for fatty acids in cytosol of intestinal mucosa, liver, myocardium, and other tissues. *Science.* **177:** 56–58.
122. Bass, N. M. 1985. Function and regulation of hepatic and intestinal fatty acid binding proteins. *Chem. Phys. Lipids.* **38:** 95–114.
123. Aas, M. 1971. Organ and subcellular distribution of fatty acid activating enzymes in the rat. *Biochim. Biophys. Acta.* **231:** 32–47.
124. Fritz, I. B. 1959. Action of carnitine on long chain fatty acid oxidation by liver. *Am. J. Physiol.* **197:** 297–304.
125. Williamson, J. R., E. T. Browning, R. Scholz, R. A. Kreisberg, and I. B. Fritz. 1968. Inhibition of fatty acid stimulation of gluconeogenesis by (+)-decanoylcarnitine in perfused rat liver. *Diabetes.* **17:** 194–208.
126. Lopes-Cardozo, M., and S. G. Van Den Bergh. 1974. Ketogenesis in isolated rat liver mitochondria. II. Factors affecting the rate of β-oxidation. *Biochim. Biophys. Acta.* **357:** 43–52.
127. Zammit, V. A. 1980. The effect of glucagon treatment and starvation of virgin and lactating rats on the rates of oxidation of octanoyl-L-carnitine and octanoate by isolated liver mitochondria. *Biochem. J.* **190:** 293–300.
128. Otto, D. A. 1984. Relationship of the ATP/ADP ratio to the site of octanoate activation. *J. Biol. Chem.* **259:** 5490–5494.
129. Groot, P. H. E., and W. C. Hülsmann. 1973. The activation and oxidation of octanoate and palmitate by rat skeletal muscle mitochondria. *Biochim. Biophys. Acta.* **316:** 124–135.
130. Frost, S. C., and M. A. Wells. 1981. A comparison of the utilization of medium and long-chain fatty acids for oxidation and ketogenesis in the suckling rat: in vivo and in vitro studies. *Arch. Biochem. Biophys.* **211:** 537–546.
131. Lieber, C. S., A. Lefèvre, N. Spritz, L. Feinman, and L. M. Decarli. 1967. Difference in hepatic metabolism of long- and medium-chain fatty acids: the role of fatty acid chain length in the production of the alcoholic fatty liver. *J. Clin. Invest.* **46:** 1451–1460.
132. Scheig, R., and G. Klatskin. 1968. Hepatic metabolism of 1-^{14}C octanoic and 1-^{14}C palmitic acids. *J. Am. Oil Chem. Soc.* **45:** 31–33.
133. Mayorek, N., and J. Bar-Tana. 1983. Medium chain fatty acids as specific substrates for diglyceride acyltransferase in cultured hepatocytes. *J. Biol. Chem.* **258:** 6789–6792.
134. Leveille, G. A., R. S. Pardini, and J. A. Tillotson. 1967. Influence of medium-chain triglycerides on lipid metabolism in the chick. *Lipids.* **2:** 461–466.
135. Jandacek, R. J., E. J. Hollenbach, B. N. Holcombe, C. M. Kuehlthau, J. C. Peters, and J. D. Taulbee. 1991. Reduced storage of dietary eicosapentaenoic and docosahexaenoic acids in the weanling rat. *J. Nutr. Biochem.* **2:** 142–149.
136. Hwang, S. G., H. Yano, and R. Kawashima. 1992. The influence of dietary medium and long chain triglycerides on growth performances and fat deposition in growing rats. *J. Nutr. Sci. Vitaminol.* **38:** 127–139.
137. Hwang, S. G., H. Yano, and R. Kawashima. 1993. Influence of dietary medium-chain and long-chain triglycerides on fat deposition and lipogenic enzyme activities in rats. *J. Am. Coll. Nutr.* **12:** 643–650.
138. Kinkela, T., F. Chanussot, A. Bach, J. P. Max, H. Schirardin, and G. Debry. 1983. Effets de régimes à triacylglycérols á chaînes moyennes et à chaînes longues chez le rat génétiquement obèse Zucker fa/fa. Composition en acides gras et en triacylglycérols du foie et des tissus adipeux. *Ann. Nutr. Métab.* **27:** 404–414.
139. Aurousseau, B., L. de Groot, and M. Vermorel. 1970.

Etude comparée de l'utilisation énergétique de régimes riches en acide caprylique ou en acides gras insaturés. *Ann. Biol. Anim. Biochim. Biophys.* **10:** 703–706.
140. Sarda, P., G. Lepage, C. C. Roy, and P. Chessex. 1987. Storage of medium-chain triglycerides in adipose tissue of orally fed infants. *Am. J. Clin. Nutr.* **45:** 399–405.
141. Maragoudakis, M. E., H. J. Kalinsky, and J. Lennane. 1975. Metabolism of octanoate and its effect on glucose and palmitate utilization by isolated fat cells. *Proc. Soc. Exp. Biol. Med.* **148:** 606–610.
142. Max, J. P., A. Bach, E. Pallier, H. Schirardin, and G. Debry. 1983. Effects of medium- and long-chain triacylglycerols on adipose tissue metabolism in the obese Zucker rat. *Int. J. Obes.* **7:** 161–165.
143. Christensen, E., T. A. Hagve, M. Gronn, and B. O. Christophersen. 1989. β-Oxidation of medium chain (C8-C14) fatty acids studied in isolated liver cells. *Biochim. Biophys. Acta.* **1004:** 187–195.
144. Carnielli, V. P., E. J. Sulkers, C. Moretti, J. L. D. Wattimena, J. B. van Goudoever, H. J. Degenhart, F. Zacchello, and P. J. J. Sauer. 1994. Conversion of octanoic acid into long-chain saturated fatty acids in premature infants fed a formula containing medium-chain triglycerides. *Metabolism.* **43:** 1287–1292.
145. Kritchevsky, D., and S. A. Tepper. 1965. Influence of medium-chain triglycerides (MCT) on cholesterol metabolism in rats. *J. Nutr.* **86:** 67–72.
146. Leveille, G. A., R. S. Pardini, and J. A. Tillotson. 1967. Influence of medium chain triglycerides on lipid metabolism in rat. *Lipids.* **2:** 287–294.
147. Pégorier, J. P., P. H. Duée, C. Herbin, P. Y. Laulan, C. Bladé, J. Peret, and J. Girard. 1988. Fatty acid metabolism in hepatocytes isolated from rats adapted to high-fat diets containing long- or medium-chain triacylglycerols. *Biochem. J.* **249:** 801–806.
148. Souza, P. F. A., and D. H. Williamson. 1993. Effects of feeding medium-chain triacylglycerols on maternal lipid metabolism and pup growth in lactating rats. *Br. J. Nutr.* **69:** 779–787.
149. Bortz, W. M., and F. Lynen. 1963. The inhibition of acetyl CoA carboxylase by long chain acyl CoA derivatives. *Biochem. Z.* **337:** 505–509.
150. Matsuhashi, M., S. Matsuhashi, and F. Lynen. 1965. Zur Biosynthese der Fettsäuren V. Die Acetyl-CoA Carboxylase aus Rattenleber und ihre Aktivierung durch Citronensaüre. *Biochem. Z.* **340:** 263–289.
151. Bach, A., T. Phan, and P. Métais. 1976. Effect of the fatty acid composition of ingested fats on rat liver intermediary metabolism. *Hormone Metab. Res.* **8:** 375–379.
152. Takase, S., A. Morimoto, M. Nakanishi, and Y. Muto. 1977. Long-term effect of medium-chain triglyceride on hepatic enzymes catalyzing lipogenesis and cholesterogenesis in rats. *J. Nutr. Sci. Vitaminol.* **23:** 43–51.
153. Demarne, Y., N. Epo, J. Flanzy, and M. J. Lecourtier. 1978. Comparison of long term lipogenic effects of two different medium-chain triglycerides (Tri C8:0 and Tri C12:0) in the growing rat. *Arch. Int. Physiol. Biochim.* **86:** 25–35.
154. Chanez, M., B. Bois-Joyeux, M. J. Arnaud, and J. Peret. 1991. Metabolic effects in rats of a diet with a moderate level of medium-chain triglycerides. *J. Nutr.* **121:** 585–594.
155. Foufelle, F., D. Perdereau, B. Gouhot, P. Ferré, and J. Girard. 1992. Effects of diets rich in medium-chain and long-chain triglycerides on lipogenic-enzyme gene expression in liver and adipose tissue of the weaned rat. *Eur. J. Biochem.* **208:** 381–387.
156. Geelen, M. J. H. 1994. Medium-chain fatty acids as short-term regulators of hepatic lipogenesis. *Biochem. J.* **302:** 141–146.
157. Kritchevsky, D., and J. L. Rabinowitz. 1966. Influence of dietary fat on fatty acid biosynthesis in rat. *Biochim. Biophys. Acta.* **116:** 185–188.
158. Hinsch, W., and W. Seubert. 1975. On the mechanism of malonyl-CoA-independent fatty-acid synthesis. Characterization of the mitochondrial chain-elongating system of rat liver and pig-kidney cortex. *Eur. J. Biochem.* **53:** 437–447.
159. Jeffcoat, R., and A. T. James. 1984. The regulation of desaturation and elongation of fatty acids in mammalians. *In* Fatty Acid Metabolism and its Regulation. S. Numa, editor. Elsevier, Amsterdam. 85–112.
160. Eckel, R. H. 1987. Adipose tissue lipoprotein lipase. *In* Lipoprotein Lipase. J. Borensztajn, editor. Evener Publisher, Chicago. 79–132.
161. Williamson, D. H. 1990. The endocrine control of adipose tissue metabolism and the changes associated with lactation and cancer. *In* The Control of Body Fat Content. J. M. Forbes, and G. R. Hervey, editors. Smith-Gordon, Lerwick. 43–61.
162. Baba, N., E. F. Bracco, and S. A. Hashim. 1982. Enhanced thermogenesis and diminished deposition of fat in response to overfeeding with diet containing medium chain triglyceride. *Am. J. Clin. Nutr.* **35:** 678–682.
163. Wall, K. M., D. Diersen-Schade, and S. M. Innis. 1994. Plasma and tissue lipids of piglets fed formula containing saturated fatty acids from medium-chain triglycerides with or without fish oil. *Am. J. Clin. Nutr.* **59:** 1317–1324.
164. Bach, A., H. Schirardin, F. Chanussot, M. Bauer, and A. Weryha. 1980. Effects of medium- and long-chain triglyceride diets in the genetically obese Zucker rat. *J. Nutr.* **110:** 686–696.
165. Ecelbarger, G. L., J. B. Lasekan, and D. M. Ney. 1991. In vivo triglyceride secretion and hepatic and plasma lipids in rats fed medium-chain triglycerides, tripelargonin, or corn-oil. *J. Nutr. Biochem.* **2:** 260–266.
166. Theuer, R. C., W. H. Martin, T. J. Friday, B. L. Zoumas, and H. P. Sarett. 1972. Regression of alcoholic fatty liver in the rat by medium-chain triglycerides. *Am. J. Clin. Nutr.* **25:** 175–181.
167. Gibbons, G. F. 1990. Assembly and secretion of hepatic very-low-density lipoprotein. *Biochem. J.* **268:** 1–13.
168. Barr, S. I., B. A. Kottke, and S. J. T. Mao. 1985. Postprandial distribution of apolipoproteins C-II and C-III in normal subjects and patients with mild hypertriglyceridemia: comparison of meals containing corn oil and medium-chain triglyceride oil. *Metabolism.* **34:** 983–993.
169. Uzawa, H., G. Schlierf, S. Chirman, G. Michaels, P. Wood, L. W. Kinsell, G. Fukuyama, N-C. Liu, and M. Coelho. 1964. Hyperglyceridemia resulting from intake of medium chain triglycerides. *Am. J. Clin. Nutr.* **15:** 365–369.
170. Hill, J. O., J. C. Peters, D. Yang, T. Sharp, M. Kaler, N. N. Abumrad, and H. L. Greene. 1989. Thermogenesis in humans during overfeeding with medium-chain triglycerides. *Metabolism.* **38:** 641–648.
171. Swift, L. L., J. O. Hill, J. C. Peters, and H. L. Greene. 1992. Plasma lipids and lipoproteins during 6 d of maintenance feeding with long-chain, medium-chain, and mixed-chain triglycerides. *Am. J. Clin. Nutr.* **56:** 881–886.
172. Mannaerts, G. P., and P. P. Van Veldhoven. 1993. Metabolic pathways in mammalian peroxisomes. *Biochimie.* **75:** 147–158.

173. Zammit, V. A. 1984. Mechanisms of regulation of the partition of fatty acids between oxidation and esterification in the liver. *Prog. Lipid Res.* **23:** 39–67.
174. Lossow, W. J., and I. L. Chaikoff. 1955. Carbohydrate sparing of fatty acid oxidation. I. The relation of fatty acid chain length to the degree of sparing. II. The mechanism by which carbohydrate spares the oxidation of palmitic acid. *Arch. Biochem. Biophys.* **57:** 23–40.
175. Metges, C. C., and G. Wolfram. 1991. Medium and long-chain triglycerides labeled with ^{13}C: a comparison of oxidation after oral or parenteral administration in humans. *J. Nutr.* **121:** 31–36.
176. Triscari, J., M. R. C. Greenwood, and A. C. Sullivan. 1982. Oxidation and ketogenesis in hepatocytes of lean and obese Zucker rats. *Metabolism.* **31:** 223–228.
177. Bach, A., G. Debry, and P. Métais. 1977. Hepatic metabolism of medium chain triglycerides. *Bibl. Nutr. Dieta.* **25:** 24–35.
178. Balasse, E., and F. Féry. 1993. Rôle des corps cétoniques dans l'homéostasie énergétique. *Nutr. Clin. Métabol.* **7:** 211–217.
179. Verkade, P. E., M. Elzas, J. Van Der Lee, H. H. de Wolff, A. Verkade-Sandbergen, and D. Van Der Sande. 1933. Untersuchungen über den Fettstoffwechsel. *Z. Physiol. Chem.* **215:** 225–257.
180. Mortensen, P. B. 1980. The possible antiketogenic and gluconeogenic effects of the ϖ-oxidation of fatty acids in rats. *Biochim. Biophys. Acta.* **620:** 177–185.
181. Lima, L. A., O. P. Gray, and H. Losty. 1987. Excretion of dicarboxylic acids following administration of medium chain triglycerides. *J. Parenter. Enterol. Nutr.* **11:** 600–601.
182. Tonsgard, J. H. 1985. Urinary dicarboxylic acids in Reye syndrome. *J. Pediat.* **107:** 79–84.
183. Gregersen, N. 1985. The acyl-CoA dehydrogenation deficiencies. *Scand. J. Clin. Lab. Invest.* **45:** 1–60.
184. Osmundsen, H., J. Bremer, and J. I. Pedersen. 1991. Metabolic aspects of peroxisomal β-oxidation. *Biochim. Biophys. Acta.* **1085:** 141–158.
185. Grego, A. V., and G. Mingrone. 1995. Dicarboxylic acids, an alternate fuel substrate in parenteral nutrition: an update. *Clin. Nutr.* **14:** 143–148.
186. Passi, S., M. Picardo, M. Nazzaro-Porro, A. Breathnach, A. M. Confaloni, and G. Serlupi-Crenscenzi. 1984. Antimitochondrial effect of saturated medium chain length (C8–C13) dicarboxylic acids. *Biochem. Pharmacol.* **33:** 103–108.
187. Christensen, E., M. Gronn, T. A. Hagve, and B. O. Christophersen. 1991. Omega-oxidation of fatty acids studied in isolated liver cells. *Biochim. Biophys. Acta.* **1081:** 167–173.
188. Whyte, R. K., D. Whelan, R. Hill, and S. McClorry. 1986. Excretion of dicarboxylic and omega-1 hydroxy fatty acids by low birth weight infants fed with medium-chain triglycerides. *Pediat. Res.* **20:** 122–125.
189. Kuhara, T., I. Matsumoto, M. Ohno, and T. Ohura. 1986. Identification and quantification of octanoyl glucuronide in the urine of children who ingested medium-chain triglycerides. *Biomed. Environ. Mass Spectrom.* **13:** 595–598.
190. Guzman, M., and M. J. H. Geelen. 1993. Regulation of fatty acid oxidation in mammalian liver. *Biochim. Biophys. Acta.* **1167:** 227–241.
191. McGarry, J. D., G. P. Mannaerts, and D. W. Foster. 1977. A possible role for malonyl-CoA in the regulation of hepatic fatty acid oxidation and ketogenesis. *J. Clin. Invest.* **60:** 265–270.
192. Bremer, J., and H. Osmundsen. 1984. Fatty acid oxidation and its regulation. *In* Fatty Acid Metabolism and its Regulation. S. Numa, editor. Elsevier Science, London. 113–154.
193. McGarry, J. D., and D. W. Foster. 1971. The regulation of ketogenesis from octanoic acid. The role of the tricarboxylic acid cycle and fatty acid synthesis. *J. Biol. Chem.* **246:** 1149–1159.
194. Schwabe, A. D., L. R. Bennett, and L. P. Bowman. 1964. Octanoic acid absorption and oxidation in humans. *J. Appl. Physiol.* **19:** 335–337.
195. Bach, A. 1978. Oxaloacetate deficiency in MCT-induced ketogenesis. *Arch. Int. Physiol. Biochim.* **86:** 1133–1142.
196. O'Donnell, J. A., and R. A. Freedland. 1980. Ketogenesis from oleate and octanoate in isolated rat hepatocytes. *J. Nutr.* **110:** 2365–2373.
197. Crozier, G. L. 1988. Medium-chain triglyceride feeding over the long term: the metabolic fate of [^{14}C]octanoate and [^{14}C]oleate in isolated rat hepatocytes. *J. Nutr.* **118:** 297–304.
198. Yeaman, S. J. 1990. Hormone-sensitive lipase. A multipurpose enzyme in lipid metabolism. *Biochim. Biophys. Acta.* **1052:** 128–132.
199. Harper, R. D., and E. D. Saggerson. 1976. Factors affecting fatty acid oxidation in fat cells isolated from rat white adipose tissue. *J. Lipid Res.* **17:** 516–526.
200. Scalfi, L., A. Coltorti, and F. Contaldo. 1991. Postprandial thermogenesis in lean and obese subjects after meals supplemented with medium-chain and long-chain triglycerides. *Am. J. Clin. Nutr.* **53:** 1130–1133.
201. Whyte, R. K., D. Campbell, R. N. Stanhope, H. S. Bayley, and J. C. Sinclair. 1986. Energy balance in low birth weight infants fed formula of high or low medium-chain triglyceride content. *J. Pediat.* **108:** 964–971.
202. Baba, N., E. F. Bracco, and S. A. Hashim. 1987. Role of brown adipose tissue in thermogenesis induced by overfeeding a diet containing medium chain triglyceride. *Lipids.* **22:** 442–444.
203. Rothwell, N. J., and M. J. Stock. 1987. Stimulation of thermogenesis and brown fat activity in rats fed medium chain triglyceride. *Metabolism.* **36:** 128–130.
204. Johnson, R. C., and R. Cotter. 1986. Metabolism of medium-chain triglyceride lipid emulsion. *Nutr. Int.* **2:** 150–158.
205. Berry, M. N., D. G. Clark, A. R. Grivell, and P. G. Wallace. 1985. The contribution of hepatic metabolism to diet-induced thermogenesis. *Metabolism.* **34:** 141–147.
206. Fisher, H., and H. Kaunitz. 1964. Effects of medium- and long-chain saturated triglycerides on blood and liver cholesterol of chicken and rats. *Proc. Soc. Exp. Biol. Med.* **116:** 278–280.
207. Newport, M. J., J. E. Storry, and B. Tuckley. 1979. Artificial rearing of pigs. 7. Medium chain triglycerides as a dietary source of energy and their effect on live-weight gain, feed: gain ratio, carcass composition and blood lipids. *Br. J. Nutr.* **41:** 85–93.
208. Hashim, S. A., and P. Tantibhedyangkul. 1987. Medium chain triglyceride in early life: effects on growth of adipose tissue. *Lipids.* **22:** 429–434.
209. Schemmel, R. 1976. Physiological considerations of lipid storage and utilization. *Am. Zool.* **16:** 661–670.
210. Yang, H., and D. M. Ney. 1994. Insulin-like growth factor-I (IGF-I) responses in rats maintained with intravenous or intragastric infusion of total parenteral nutrition solutions containing medium- or long-chain triglyceride emulsions. *Am. J. Clin. Nutr.* **59:** 1403–1408.

211. Saxena, S. C., A. Vendelmans-Starrenburg, and R. O. Vles. 1972. Effects of feeding medium chain glycerides to rats for 13 weeks. *Nutr. Metab.* **14:** 362–370.
212. Woollett, L. A., D. K. Spady, and J. M. Dietschy. 1989. Mechanisms by which saturated triacylglycerols elevate the plasma low density lipoprotein-cholesterol concentration in hamsters. *J. Clin. Invest.* **84:** 119–128.
213. Mabayo, R. T., M. Furuse, K. Kita, and J. Okumura. 1993. Improvement of dietary protein utilization in chicks by medium chain triglyceride. *Br. Poultry Sci.* **34:** 121–130.
214. Yeh, Y. Y., L. B. Klein, and P. Zee. 1978. Long and medium chain triglycerides increase plasma concentrations of ketone bodies in suckling rats. *Lipids.* **13:** 566–571.
215. Bray, G. A. 1991. Obesity, a disorder of nutrient partitioning: the MONA LISA hypothesis. *J. Nutr.* **121:** 1146–1162.
216. Osteroth, D. 1971. Glyceride mittelkettiger Fettsaüren. *Seifen-Öle-Fette-Wachse.* **7:** 187–189.
217. Spielmann, D., U. Bracco, H. Traitler, G. Crozier, R. Holman, M. Ward, and R. Cotter. 1988. Alternative lipids to usual omega 6 PUFAS: gamma-linolenic acid, alpha-linolenic acid, stearidonic acid, EPA, etc. *J. Parenter. Enteral. Nutr.* **12:** 111S–123S.
218. Bray, G. A., and D. S. Gray. 1988. Treatment of obesity: an overview. *Diabetes Metab. Rev.* **4:** 653–679.
219. Wadden, T. A., J. A. Sternberg, K. A. Letizia, A. J. Stunkard, and G. D. Foster. 1989. Treatment of obesity by very low caloric diet, behavior therapy, and their combination: a five year perspective. *Int. J. Obes.* **13**: 39–46.
220. Kaunitz, H., C. A. Slanetz, R. E. Johnson, V. K. Babayan, and G. Barsky. 1958. Nutritional properties of the triglycerides of saturated fatty acids of medium chain-length. *J. Am. Oil Chem. Soc.* **35:** 10–13.
221. Reeves, P. G., F. H. Nielsen, and G. C. Fahey. 1993. AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition ad hoc Writing Committee on the reformulation of the AIN-76A rodent diet. *J. Nutr.* **123:** 1939–1951.
222. National Academy of Sciences. 1989. Recommended Dietary Allowances. 10th Revised Edition, Washington, DC.