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Influence of Dietary Medium-Chain Triglycerides on the Development of *N*-Methylnitrosourea-induced Rat Mammary Tumors[1]

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ABSTRACT

The mammary tumor-promoting effects of a high-fat (HF) diet (23%, w/w) containing a 3:1 mixture of medium-chain triglycerides (MCT) and corn oil were compared with those of a low-fat (LF) corn oil diet (5%) and a HF:corn oil diet (23%, w/w). It was found that the ingestion of MCT in a HF diet resulted in no detectable tumor-promoting effects in animals initiated with the potent mammary carcinogen *N*-nitrosomethylurea. Total palpable mammary tumor incidence was 60% in the HF:corn oil plus MCT group, 66% in the LF:corn oil group, and 87% in the HF:corn oil group ($p < 0.03$ and $p < 0.06$, respectively). However, when palpable adenocarcinomas only were counted, differences in incidence between groups were not statistically significant, HF:MCT (57%) *versus* HF:corn oil (77%), $p < 0.08$. Mean time to first tumor (days) was 122 ± 40 (S.D.) in the MCT, 117 ± 36 in the LF:corn oil groups, and 86 ± 23 in the HF:corn oil group. The cumulative tumor incidence curves were similar for the MCT and LF:corn oil groups ($p < 0.9$); however, both curves were significantly different from that of the HF:corn oil group ($p < 0.0099$). No differences were found in tumor multiplicity, tumor size, or body weight gain in any of the treatment groups. Assay of serum total cholesterol and triglycerides showed that consumption of 23% corn oil diet significantly depressed serum cholesterol (but not triglyceride) levels compared to the LF:5% corn oil- and the HF:MCT-containing diets. Analysis of serum fatty acid profiles indicated that animals fed 23% corn oil exhibited twice the amount of linoleic acid ($C_{18:2}$) as did those fed either 5% corn oil or MCT. Differences in other fatty acids were of a much lesser magnitude.

These results indicate that the mammary tumor-promoting effect of a HF diet can be diminished by substituting saturated MCT for the more common longer-unsaturated-chain triglycerides. In addition, they suggest an association between promotion of mammary cancer and elevated levels of linoleic acid in serum lipids.

INTRODUCTION

Numerous epidemiological and experimental studies suggest that dietary fat is an important determinant of breast cancer risk (19, 42). Studies in laboratory animals have shown that the influence of dietary fat is exerted primarily on the promotion stage of mammary carcinogenesis (11, 16), a finding which may be reflected in the fact that the association between fat intake and increased risk is most pronounced in women over 40 years old (37).

Moreover, experimental studies by Carroll *et al.* (9, 10, 29) and others (15, 20, 25–27, 32, 41, 45) have shown that the kind as well as the amount of fat ingested determines the rate of development of chemically induced and transplantable mammary tumors. In these studies, it was shown that the presence of a certain proportion of essential polyunsaturated fatty acids appears to be required for optimal tumor-enhancing effects and that HF[3] diets containing coconut oil [which consists primarily of short- and medium-chain saturated fatty acids and a small quantity (<2%) of LA,] lack the ability to promote mammary tumor development when compared to HF diets rich in polyunsaturated fatty acids.

As the above evidence suggests, the degree of saturation and possibly the chain length of constituent fatty acids can modify the effect of HF diets. Accordingly, it appeared appropriate to test the effects of tumor development of a HF diet based on a synthetic derivative of coconut oil, namely, MCT.[4] Relative to coconut oil, MCT have the advantage that their physiological and biological properties are well documented (4) and that they have a more restricted and essentially invariant fatty acyl group profile.

In the present study, therefore, the NMU-induced rat mammary tumor model was used to compare the tumor-promoting effects of diets containing low (5%) and high (23%) levels of corn oil with a HF diet (23%) containing MCT:corn oil (3:1). Since MCT contains no LA, corn oil is added as a supplement to ensure adequate essential fatty acid intake. Moreover, because MCT have been reported to alter serum lipids (2, 4), serum cholesterol and triglycerides were also assessed.

MATERIALS AND METHODS

Experimental Protocol

Tumor Induction. Ninety inbred, virgin, female F344 rats, 28 days old (Charles River Breeding Laboratories, North Wilmington, MA), were maintained on the standard NIH-07 diet (Zeigler Bros., Gardners, PA) (6) until 50 days of age. All animals were then randomized into 3 groups of 30 animals each by recognized procedures (21) in ordet to equalize initial mean weights. On Day 50 of age, all animals received a single dose of NMU (50 mg/kg body weight) by tail vein injection. The NMU (Ash Stevens, Inc., Detroit, MI) was dissolved in 5–10 drops of 3% acetic acid, and NMU was brought up to volume in distilled H_2O yielding a stock solution of 10 mg/ml administered within 2 hr of formulation (15).

Diet Administration. Two days after carcinogen administration, animals were transferred to experimental diets; the animals remained on experimental diets for the duration of the experiment.

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[3] The abbreviations used are: HF, high-fat diet; FAME, fatty acid methyl ester; LA, linoleic acid; LF, low-fat diet; MCT, medium-chain triglyceride; NMU, *N*-nitrosomethylurea.

[4] Medium-chain fatty acids are obtained by hydrolysis of coconut oil [$C_{8:0}$ (<2%); $C_{8:0}$ (7%); $C_{10:0}$ (6%); $C_{12:0}$ (50%); $C_{14:0}$ (20%)] followed by fractional distillation of the resulting fatty acid mixture to obtain a mixture of $C_{8:0}$ (1 to 2%); $C_{8:0}$ (65 to 75%); $C_{10:0}$ (25 to 35%); $C_{12:0}$ (1 to 2%) fatty acids. The medium-chain fatty acids are then esterified to glycerol in the presence of a zinc catalyst to generate the triglyceride (4).

The HF and LF Diets

Adjusted HF Diet. The diet used in these experiments is based on the recommendations of the Committee on Laboratory Animal Diets of the National Academy of Sciences (5, 38, 49) with slight modifications.

It has been found in our laboratory and those of others that rats adjust their food intake so that similar energy intake is maintained despite the fact that diets may differ substantially in energy density. Hence, animals will eat quantitatively less of HF diet than a LF diet. Consequently, unless the proportions of the other components in the diet are adjusted, animals fed a HF diet will take in substantially less protein, fiber, vitamins, minerals, etc., than did those fed a LF diet. The adjustment recommended by the Committee on Laboratory Animal Diets was therefore incorporated into our experimental protocol. The adjusted diet formulation ensured that animals fed a HF diet took in the same amount of vitamins, minerals, and fiber as did animals on the LF diet and that adequate antioxidant activity was present in the form of vitamin E, selenium (as a cofactor of glutathione peroxidase), and vitamin A in each dietary group. The increase in fat in the HF diet was compensated for by a decrease in the amount of starch:dextrose (Table 1). The HF and LF diets consisted of 23% and 5.0% corn oil. These percentages were designed to mimic the American [high-risk] diet [40 to 45% of total calories as fat] and the Japanese [low-risk] diet [13% of total calories as fat during the years 1957 to 1959 (42)].

LF Diet. The LF diet was designed to provide approximately 5 to 6 calories of fat per day, based on an estimated consumption of 45 to 50 calories per day, (14) or approximately 12% of total calories. The HF diet, on the other hand, provided approximately 20 to 21 calories per day as fat or 45% of total calories. All dietary ingredients were obtained from Dyets, Inc. (Bethlehem, PA), and were mixed in-house in our diet kitchen. Diets were formulated in 4-kg lots, in plastic bags, and stored at 4° in the dark until used.

Animals were housed 3 to a cage in plastic cages covered with filter tops in a room controlled for temperature [24° ± 2° (S.D.)], light (12-hr cycle), and humidity (50%) and were given diets (in powdered form) and tap water *ad libitum*. Stainless steel J-type powder feeders (Lab Products, Inc., Rochelle Park, NJ) were used to prevent scattering of powdered food.

Food Consumption

Food consumption was measured to assure that the different types of fat did not alter food consumption patterns. Five animals ages 110 to 120 days from each treatment group were placed into individual metabolism cages, and food intake was quantified for 4 days after an adjustment period of 3 days.

Observation Schedule

At weekly intervals beginning 4 weeks after NMU injection, each rat was weighed, and the position and date of appearance of palpable tumors were recorded.

Table 1

Composition of defined, semipurified diets

Ingredient	LF:corn oil (g)	Adjusted HF	
		Corn oil (g)	MCT[a] (g)
Casein	20.0	23.5	23.5
Corn starch	52	32.9	32.9
Dextrose	13	8.30	8.30
Fat			
Corn oil	5	23.52	5.88
Medium-chain triglyceride			17.64
DL-Methionine	0.3	0.35	0.35
Choline bitartrate	0.2	0.24	0.24
Alphacel	5	5.9	5.9
(AIN-76) vitamin mix	1.0	1.18	1.18
(AIN-76) mineral mix	3.5	4.11	4.11
Total	100.0	100.00	100.00
Energy value (kcal/g)	3.89	4.73	4.73

[a] Corn oil (5%) is added to assure adequate amounts of essential fatty acids.

Histopathology

Approximately 22 weeks after NMU administration, all rats were sacrificed by decapitation, and serum was collected following centrifugation of whole blood. Serum was stored at −20° until assayed. Palpable tumors were excised fixed in buffered formalin, blocked in paraffin, and then sectioned and stained with hemotoxylin and eosin. Histological diagnosis of mammary tumors (by Y. Maeura) was based on the criteria outlined by Young and Hallowes (51).

Biochemistry

Nonfasting serum total cholesterol and triglycerides were determined by the use of a Gilford 3500 computer-directed autoanalyzer. Total cholesterol was determined using an enzymatic procedure described by Flegg (22) and others (1, 43, 44). Triglycerides were determined using enzymatic procedures published by Pinter *et al.* (39). Both determinations were carried out using Worthington reagents (Worthington Diagnostics, Freehold, NJ).

Serum Fatty Acid Profiles

Sera (30 per treatment group) were pooled to generate 4 to 5 representative samples per treatment group and extracted using a modified Radin (40) extraction procedure (48). For extraction, 1-ml aliquots were diluted with 3 ml of 7% aqueous sodium sulfate (saturated with hexane). The mixture was extracted once with hexane:isopropyl alcohol (18 ml, 3:2, v/v) (27). The aqueous layer was then reextracted twice with hexane:isopropyl alcohol (18 ml, 7:2, v/v). All 3 organic phases were collected, combined, and evaporated under nitrogen gas to yield the total serum lipid extract. The efficiency of extraction was determined by following the extraction of glycerol tri[1-^{14}C]palmitate and di[1-^{14}C]-palmitoyl-L-α-phosphatidylcholine, (New England Nuclear, Boston, MA) from serum samples to which these radioactive tracers were added. The extraction efficiency was >95%.

The fatty acid composition of the serum extract was determined by gas:liquid chromatography of a methyl ester preparation. The total lipid extract was transmethylated by heating the sample in 2 ml benzene, with 2 ml boron trifluoride:methanol reagent (Supelco, Inc., Bellefonte, PA) for 30 min at 90° (37). The completeness of the transmethylation was determined by following the conversion of the radiolabeled lipids to their respective radioactive methylpalmitates. The conversion was monitored by thin-layer chromatography. FAME were then analyzed by gas chromatography (Hewlett-Packard, 7610A) using a 6-ft x 0.25-inch 10% SP 2330-on-Chromosorb W-AW column (Supelco, Inc.). Fatty acids were identified by comparison of retention volumes with authentic methyl ester standards (Nu-Chek-Prep, Inc., Elysian, MN). A reference standard containing the relative amount of each FAME in coconut oil and corn oil was obtained from Nu-Chek Prep., Inc. This standard was chromatographed at various times during the analysis to ascertain whether or not changes in retention time or peak shape occurred due to instrumental changes during the analysis. The peak areas were calculated by multiplying the peak height by the width at half-height. Each area was corrected by a factor obtained from the detector yield of known amounts of standards. The percentage of each FAME was then calculated by dividing the individual peak area by the total area under all the peaks.

Statistical Evaluation of Data

Mammary tumor data were analyzed with the aid of a FORTRAN Program provided by Dr. J. J. Gart of the National Cancer Institute (23). This program, based on the life tables method of Kaplan and Meier, determines in a variety of ways whether the cumulative tumor incidence profiles of the 3 treatment groups derive from the same or different distributions. Fischer's exact test (one tailed) (23) was used to assess

differences in final tumor incidence. Difference in tumor multiplicity were assessed by analysis of variance after log transformation of the tumor count data. Analysis of weight gain data was by the use of a SAS program for analysis of variance with repeated measures (24). Serum cholesterol and triglyceride data were analyzed by one-way analysis of variance.

RESULTS

Pathology. With the exception of mammary tumors, no gross changes in the major organs or organ systems were seen. Mammary tumors were either adenocarcinomas or fibroadenomas with the latter varying in frequency from 3 to 10% of the total animals in each group. One mammary sarcoma was found in the 23% corn oil group. None of the animals died of extraneous causes, and there were no unscheduled sacrifices due to necrotizing tumors.

Nonpalpable (microscopic) adenocarcinoma were relatively rare occurring in 7, 8, and 2 animals in the 23% corn oil, 5% corn oil, and corn oil plus MCT groups, respectively.

Occasionally, palpable tumors appeared during the course of the experiment and disappeared before termination. This occurred in 4, 3, and 5 animals in the 23% corn oil, 5% corn oil, and corn oil plus MCT groups, respectively. These tumors were conducted in the life tables analyses but not counted when final tumor incidences were tabulated.

Tumor Incidence, Latency, and Multiplicity. Animals fed the MCT-containing diet exhibited a significantly lower total mammary tumor incidence when compared to animals fed a HF:corn oil diet (60 *versus* 87%, $p < 0.03$) (Table 2). However, when palpable adenocarcinomas alone were counted the difference in incidence failed to attain statistical significance (57 *versus* 77%, $p < 0.08$). Likewise, when HF:corn oil- and LF:corn oil-fed animals were compared in terms of total palpable mammary tumors, statistical significance was barely missed (66 *versus* 87%, $p > 0.06$); however, when only palpable adenocarcinomas were counted, differences in tumor incidence did not reach the level of statistical significance (60 *versus* 77%, $p < 0.10$.)

Analysis of time-to-first-tumor curves (Chart 1) indicated clearly that mammary tumors appeared more rapidly in the HF:corn oil group than in the HF:MCT and the LF:corn oil groups. The stepwise survival curves exhibited by the latter 2 groups were indistinguishable, whereas there was a significant delay in tumor appearance in these groups when compared to the HF:corn oil curve. The median times to first tumor in the HF:corn oil, HF:MCT, and LF:corn oil groups were 90, 120, and 120, respectively (Table 3). Tumor multiplicity was similar in each group (Table 4), and no difference in tumor size was seen in the different treatment groups (data not shown).

Biochemistry. With regard to serum lipid concentrations, mean nonfasting cholesterol levels were significantly lower in animals fed 23% corn oil, compared to those fed either 5% corn oil or the corn oil plus MCT diet. No significant differences were found in serum triglycerides for any of the 3 treatment groups (Table 5).

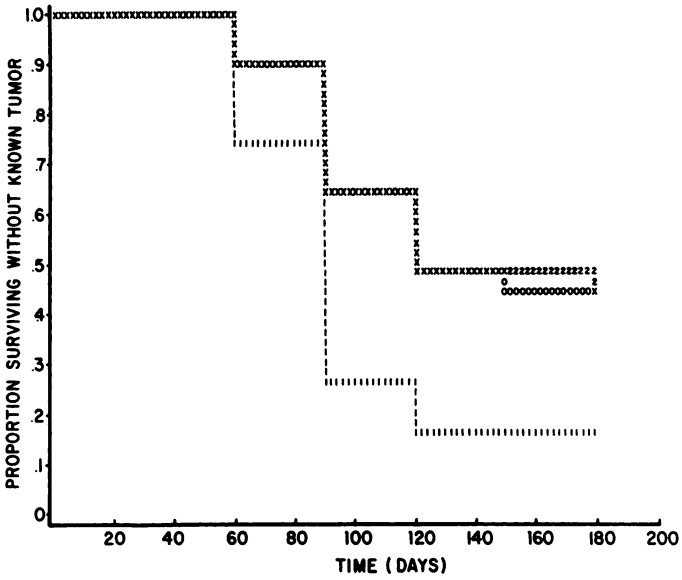

Chart 1. Kaplan-Meier life tables curves for cumulative mammary tumor incidence. *0*, 18% MCT + 6% corn oil; *1*, 23% corn oil; *2*, 5% corn oil; ×, overlapping lines. Tests for overall trend, Cox's test for adjusted trends ($p < 0.0035$). Pairwise comparisons: Cox's test (conservative): 23% corn oil *versus* 5% corn oil ($p < 0.0099$); 23% corn oil *versus* MCT ($p < 0.0086$); 5% corn oil *versus* MCT ($p < 0.9$).

Table 3

Influence of MCT on the latent period of NMU-induced mammary tumors

Dietary fat	% of fat	N[a]	Mean latent period (days post-induction)	Median latent period (days)
Corn	23	30	86 ± 23[b]	90
Corn	5	30	117 ± 36	120
Corn + MCT	6 + 18	30	122 ± 40	120

[a] *N*, no. of animals at risk.
[b] Mean ± S.D. of days to first tumor.

Table 2

Influence of MCT on the incidence of NMU-induced mammary tumors[a]

			Adenocarcinoma		Fibroadenoma		Total tumors[c]	
Dietary fat	% of Fat	N[b]	Tumor incidence (%)	No. of tumor-bearing animals/no. of animals at risk	Tumor incidence (%)	No. of tumor-bearing animals/ no. of animals at risk	Tumor incidence (%)	No. of tumor-bearing animals/no. of animals at risk
Corn	23	30	77	23/30	10	3/30	87	26/30
Corn	5	30	60	18/30	6	2/30	66	20/30
Corn + MCT	6 + 18	30	57	17/30	3	1/30	60	18/30

[a] Palpable tumors only.
[b] *N*, no. of animals at risk.
[c] Total tumors: 23% corn oil *versus* 5% corn oil, $p = 0.062$; 23% corn oil *versus* corn oil + MCT, $p = 0.03$; 5% corn oil *versus* corn + MCT, not significant. All adenocarcinoma comparisons are not significant.

The fatty acid profiles of serum lipids differed primarily in the quantity of LA ($C_{18:2}$) present. Animals fed 23% corn oil diets exhibited twice the amount of LA as those fed 5% corn oil- or MCT-containing diets. Differences in $C_{14:0}$, $C_{16:0}$, $C_{16:1}$, $C_{18:3}$, and $C_{20:4}$ fatty acids were also noted (Table 6), although these were of a lesser degree of magnitude.

Animal Weights. Animal weight gains were similar in each group (Table 7), indicating that differences in type or quantity of dietary fat did not alter food consumption patterns. Direct measurement of food consumption confirmed this finding. LF animals consumed 11 to 12 g/day, while HF animals consumed 8 to 10 g/day.

DISCUSSION

This study indicates that a HF diet containing high levels of MCFAs does not enhance the development of mammary tumors in contrast to a HF diet containing the more common long-chain fatty acids. The tumor-promoting effects of a HF:corn oil diet was clearly evident when assessed in terms of latency or time of appearance. However, when assessed in terms of tumor incidence, significance could be obtained only if total (adenocarcinomas plus fibroadenomas) palpable tumors were included in the analysis. No differences were seen in tumor multiplicity or size in any of the treatment groups. The reasons for this variability in end-point measures are unclear. Chan *et al.* (15), using the same model and dose of carcinogen, reported tumor incidences of 85% (25% corn oil) and 33% (5% corn oil). However, when comparing the study of Chan *et al.* and our study, several important procedural differences emerge. First, they included both palpable and nonpalpable (observable only upon histological examination) adenocarcinomas in their computations, and no breakdown of the 2 classes of carcinomas was given. In the present study, only palpable tumors were assessed. Test diets were administered from Day 21 on, wheres in our study test diets were administered on Day 57 of age, 2 days after carcinogen administration. Third, the diets differed with regard to the type of carbohydrate used. Our diet was based on a starch:dextrose combination, whereas Chan *et al.* used dextrose as the sole source of carbohydrate. This may be of significance since complex and simple carbohydrates have been reported to exert differential effects on chemically induced mammary tumorigenesis (27).

It also is noteworthy that an inherent between-experiment variability exists in the mammary tumor model. The influence of this intrinsic variability can be decreased by increasing the total number of animals at risk, decreasing the carcinogen dose, increasing the difference in total fat intake between LF and HF groups, and assessing tumor development by as many different measures as possible. However, as of the present, no general consensus exists as to which experimental procedures confer the greatest degree of reproducibility and validity.

Our failure to find any differences in tumor multiplicity between

Table 4

Influence of MCT on the incidence of NMU-induced mammary tumors

Dietary fat	% of fat	No. of adenocarcinomas/total no. of animals with 1 or more adenocarcinomas
Corn	23	0.48 ± 0.48[a, b] (1.61)[c]
Corn	5	0.43 ± 0.56 (1.53)
Corn + MCT	6 + 18	0.58 ± 0.61 (1.78)

[a] Least square mean ($\log_e$) ± S.D.
[b] All pairwise comparisons not significant (by one-way analysis of variance).
[c] Numbers in parentheses, antilog$_e$.

Table 7

Mean animal weights (cumulative)

Wt (wk post-induction)	Animal wt (g)		
	Corn (23%)	Corn (18%) + MCT (6%)	Corn (5%)
0	100 ± 4[a, b]	100 ± 4	101 ± 3
4	137 ± 6	137 ± 7	135 ± 6
8	163 ± 9	161 ± 9	159 ± 7
12	169 ± 10	166 ± 10	165 ± 6
16	175 ± 10	176 ± 10	171 ± 8
20	176 ± 10	178 ± 12	175 ± 9
22	178 ± 11	178 ± 14	176 ± 10

[a] Mean ± S.D.
[b] All comparisons of weight curves not significant by analysis of variance.

Table 5

Influence of various dietary fats on serum lipid concentrations

Dietary fat	% of fat	N[a]	mg/100 ml					
			Cholesterol			Triglycerides		
			Mean ± S.D.	Median	Range	Mean ± S.D.	Median	Range
Corn	23	30	80 ± 16[b, c]	81	53–137	117 ± 43[c]	116	38–199
Corn	5	30	108 ± 15	107	81–146	112 ± 46	98	63–303
Corn + MT	6	30	107 ± 15	109	66–131	142 ± 83	117	65–420

[a] N, no. of animals at risk.
[b] Corn oil (20) *versus* MCT, $p < 0.0001$; corn oil (20) *versus* corn oil (5), $p < 0.0001$.
[c] All pairwise comparisons not significant (by one-way analysis of variance).

Table 6

Comparison of serum lipid fatty acid profiles in animals fed diets varying in type and amount of fat

Dietary fat	Fatty acid %[a]							
	14:0	16:0	16:1	18:0	18:1	18:2	18:3	20:4
Corn oil (23%)	[b]	18.4 ± 0.9[c]	[b]	19.1 ± 1.5	9.8 ± 1.2	28.5 ± 1.7	[b]	23.5 ± 2.2
Corn oil (5%)	0.5 ± 0.1	22.9 ± 0.7	1.2 ± 0.2	17.6 ± 3.9	15.1 ± 1.8	13.2 ± 1.3	0.5 ± 0.3	29.1 ± 4.4
Corn oil (6%) + MCT (18%)	0.7 ± 0.2	24.5 ± 5.0	1.1 ± 0.3	19.4 ± 1.4	11.4 ± 2.6	13.3 ± 2.7	[b]	28.2 ± 0.9

[a] Difference between sum of fatty acid percentages in each row and 100% represents sum of minor components not shown in table.
[b] Not detectable.
[c] Mean ± S.D. (4 samples/group).

animals fed the LF:corn oil and HF:MCT diets is of interest in light of the studies of Carroll *et al.* (9, 29) using the 7,12-dimethylbenz(*a*)anthracene model. Carroll *et al.* (9) reported that a diet containing 3% sunflower seed oil plus 17% coconut oil promoted mammary tumorigenesis to the same extent as did a diet containing 20% sunflower oil (75% LA). However, it is noteworthy that tumor enhancement in this case was seen only when assessed in terms of tumor multiplicity; no differences were seen in terms of tumor incidence or latency. On the basis of this experiment, it was suggested that there were 2 requirements for mammary tumor promotion by dietary fat, a small amount of LA together with an overall HF intake.

This line of research was extended by Hopkins *et al.* (29), who fed animals diets consisting of 17% coconut oil supplemental either with 3% methyl LA or 3% methyl oleate and compared them with animals fed 20% sunflower seed oil. It was found, again primarily with regard to tumor multiplicity, that animals fed the coconut oil plus LA diet exhibited tumor yields similar to those fed 20% sunflower seed oil.

On the basis of the above studies, one might expect a stimulation of tumor development in the corn oil:MCT group, since over 2.5% LA and a total of 23% fat was present in the diet, but this was not the case. One reason for the discrepancy between our and Carroll's results is that different tumor models were used. Another is that, because the fatty acyl group profile of coconut oil differs considerably from that of MCT, the effects of the 2 oils may not be comparable. Also, while MCT have been shown to influence essential fatty acid metabolism (3, 31), it remains to be demonstrated whether coconut oil has similar effects. Lastly, the methyl ester of $C_{18:2}$ was used in the Hopkins study, whereas in the present study $C_{18:2}$ was ingested in the form of a mixed triglyceride molecule. Since the transport and absorption of fatty acids are, at least in part, dependent on the form in which they are ingested (17), direct comparison of the 2 studies must be viewed with caution.

Possible mechanisms underlying the observed effects of the MCT-containing diet may be either direct or indirect. A direct mechanism can be envisaged based on the unique physicochemical and biological properties of MCT. Although lipid in nature, MCT are absorbed and transported by the body in a manner more characteristic of carbohydrates than of lipids. In contrast to long-chain fatty acids, MCT do not enter lymph or chylomicrons, are not incorporated into membranes, and are rapidly oxidized by the mitochondria via a carnitine-independent, rather than a carnitine-dependent, mechanism (2, 4, 7). Hence, because of these unique physiological properties, the HF:MCT diet may exert biological effects more like those of a LF than a HF diet.

MCT may also act via indirect mechanisms involving actions at hormone receptors and/or essential fatty acid metabolism. With regard to the former, it has been shown by Knazek *et al.* (33) and Cave and Erikson-Lucas (13) that feeding MCT to rats lowered the number of prolactin receptors in both hepatic tissue and mammary tumors. Since prolactin is a recognized promoting substance in mammary tumorigenesis (18, 30), its tumor growth-promoting effects could be attenuated by limiting, via dietary means, the number of receptors in the target organ available for activation by circulating prolactin. With regard to the latter, there have been several reports that MCT influence essential fatty acid metabolism (3, 31). MCT, for example, have been shown to exert a sparing effect on the LA requirement for relief of the symptoms of essential fatty acid deficiency. These findings are of particular interest since essential fatty acids and their metabolism to prostaglandins appear to play a role in both the HF effect and the essential fatty acid deficiency syndrome (12, 25, 34–36).

Changes in serum fatty acid profiles were seen mainly in the LA content, which was significantly elevated in the serum of the HF corn oil group. The fact that only LA, of all the major fatty acids present in serum, was elevated in 23% corn oil animals, is most probably a reflection of its status as an essential fatty acid (that is it cannot be synthesized by the body and therefore must be consumed in the diet) (34). Since Δ^6-desaturase (the rate-limiting enzyme in the pathway from LA to arachidonic acid and ultimately the whole range of prostaglandins) is subject to inhibition by long-chain fatty acids (8, 50), consumption of a HF:corn oil diet may suppress the activities of the fatty acid desaturases and/or chain-elongating enzymes and thereby slow the conversion of LA to its various metabolites. However, in the absence of any direct data on the fatty acid desaturases, one can only speculate on the metabolic basis for the observed differences in serum fatty acid patterns reported in the present study.

The intake of MCT has been associated with reductions in tissue and serum cholesterol (4). In this study, animals receiving the MCT-containing HF diet exhibited significantly higher, rather than lower, serum cholesterol levels compared to animals receiving 23% corn oil. The reason for this is uncertain. It may be due to the fact that MCT limit cholesterol deposition in tissues (4) and that the observed high serum cholesterol levels may therefore be due to a reapportionment of cholesterol from the tissue to the serum compartments. The suppression of serum cholesterol levels by diets high in polyunsaturated fats such as corn oil is a well-established phenomenon, although the mechanism by which this occurs is uncertain (46, 47).

In conclusion, this study emphasizes the importance of viewing dietary lipids not only in terms of their physicochemical characteristics, *i.e.*, chain length, degree of saturation, and levels of isomerization, but also in terms of their specific physiological roles in body metabolism. In this regard, MCT, which are unique among triglycerides in their mode of absorption and transport, should provide a valuable tool for further exploration of the role of dietary fat in breast cancer development.

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