

did not exceed 11 carbon atoms. However, the identification of a number of compounds with more than 11 carbon atoms, e.g., 2-dodecenoic acid, indicates that an apparent double bond migration may take place when triolein is treated under the conditions used in this study. The possibility of double bond migration in trilinolein, treated under conditions identical to those reported here, has been previously reported by Thompson et al. (9).

Three terminally unsaturated aldehydes and the three corresponding terminally unsaturated acids were identified for the first time in the VDP of an oil system. One possible mechanism for the formation of one of these terminally unsaturated compounds, starting from the 11-hydroperoxide of oleic acid, is given in Figure 6. Levy and Paul (16) have demonstrated the possibility of oxidation of a carbon atom,  $\beta$ - to a carboxylate group. A number of other possible mechanisms for the formation of these compounds exists. This area deserves additional study.

The lack of a large number and large amount of dienals, especially the 2,4-decadienals, demonstrates the limited extent of dehydrogenation during thermal oxidation of triolein, and helps explain the lack of a strong, deep-fat fried aroma in the treated triolein.

#### ACKNOWLEDGMENTS

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## ✿ Biochemistry of Unsaturated Fatty Acid Isomers<sup>1</sup>

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#### ABSTRACT

Recognition that catalytic hydrogenation changes the configuration and position of double bonds and alters the physical properties of unsaturated fats prompted numerous early investigations on the biochemical effects of "trans isomers." Recent research has provided data on positional isomer metabolism. Some aspects of fatty acid isomer metabolism are now reasonably well understood, but other issues are not resolved. Human and animal data have provided good evidence that isomers in partially hydrogenated oils are well adsorbed and incorporated into all organs and tissues. Analyses of human tissues also indicate that hydrogenated oils are the major source of fatty acid isomers in the US diet. Tissue composition data combined with isolated enzyme studies and isotope tracer experiments with whole organisms show unquestionably that structural differences between various fatty acid isomers influence specific biochemical transformations. Examples are differences in the reaction rates and/or specificities of acyl transferase, lipase, desaturase and cholesteryl esterase/hydrolase for various positional fatty acid isomers. Isolated microsomes and mitochondria also have been used to identify differences in acyl CoA activation, oxidation, and elongation of positional isomers. In addition, isotope tracer experiments show that preferential metabolism of individual positional isomers occurs in vivo. In vivo studies with hydrogenated vegetable oil diets containing adequate levels of linoleic acid produced no obvious physiological

changes. Experiments with specific polyunsaturated isomers have produced changes in blood cell properties, pulmonary weight, linoleic acid requirements and tissue lipid composition. These changes may be related to a number of factors such as membrane fluidity and permeability, cell function, synthesis of arachidonic acid, homo-gamma-linoleic acid or prostaglandins. Whether differences in the biochemistry of fatty acid isomers are desirable or undesirable and whether these differences contribute to long-term or subtle effects important to the etiology of atherosclerosis and cancer are not resolved.

#### INTRODUCTION

Research on the biochemistry of unsaturated fatty acid isomers began in the 1930s (1) and dealt with the deposition in rat tissue of "isoleic acid" present in hydrogenated oils. Since that time, interest in the biochemistry and metabolism of fatty acid isomers has paralleled the steady increase in consumption of partially hydrogenated vegetable and marine oils.

During the 1960s, analytical methods were developed and used to identify a wide range of both *cis* and *trans* positional isomers in partially hydrogenated oils that are formed as a side reaction in the hydrogenation process. *cis* and *trans*

<sup>1</sup> Presented at the 73rd AOCS annual meeting, Toronto, 1982.

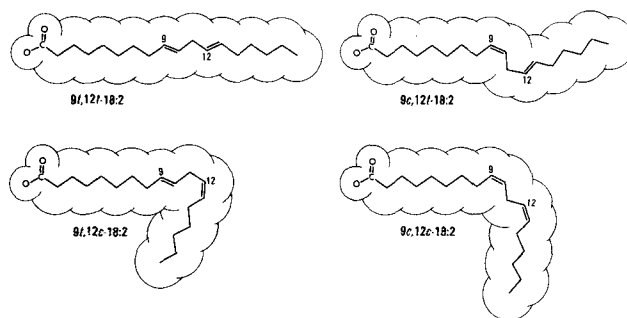
**TABLE I**  
Enzyme Studies with Monounsaturated Fatty Acid Isomers

Reaction class or enzyme	Fatty acid isomer(s)	Reference
Pancreatic lipase	$\Delta 2-16$ <i>cis</i> -18:1	15
Acyl CoA activation	$\Delta 4-15$ <i>trans</i> -18:1	16
	$\Delta 4-17$ <i>cis</i> -18:1	17
$\beta$ -oxidation	$\Delta 4-16$ <i>cis</i> and <i>trans</i> 18:1	18
	$\Delta 8-11$ <i>cis</i> and <i>trans</i> 18:1	19
Phosphatidylcholine: acyl transferase	$\Delta 2-17$ <i>cis</i> -18:1	20
	$\Delta 2-17$ <i>trans</i> -18:1	21
	9 <i>t</i> -18:1	22
	9 <i>t</i> -18:1, 11 <i>t</i> - and 11 <i>c</i> -20:1, 13 <i>t</i> and 13 <i>c</i> -22:1, 9 <i>t</i> -16:1	23
Cholesterol: acyl transferase	6 <i>c</i> -, 9 <i>c</i> -, 11 <i>c</i> -, 15 <i>c</i> -18:1	24
	9 <i>t</i> -, 11 <i>t</i> -, 11 <i>c</i> -20:1	25
Cholesterol ester synthetase	13 <i>c</i> -22:1	26
Cholesteryl esterase	9 <i>t</i> -, 11 <i>t</i> -, 11 <i>c</i> -18:1	27
Cholesterol ester hydrolase	$t$ -16:1, $t$ , $t$ -18:2	28
Desaturase	9 <i>t</i> -, 11 <i>t</i> -, 11 <i>c</i> -18:1	29
	$\Delta 2-17$ - <i>cis</i> 18:1	30
	12 <i>c</i> -18:1	31
	$\Delta 4-15$ <i>trans</i> -18:1	32
	$\Delta 8-14$ <i>cis</i> - and <i>trans</i> -18:1, 12 <i>t</i> - and 12 <i>c</i> -17:1, 5 <i>t</i> -16:1, 5 <i>t</i> -17:1, 5 <i>t</i> -18:1	33
Elongation	$\Delta 4-11$ <i>cis</i> -18:1	34
	$\Delta 4-15$ <i>trans</i> -18:1	35

**TABLE II**  
Enzyme Studies with Polyunsaturated Fatty Acid Isomers

Reaction class or enzyme	Fatty acid isomer	Reference
Cholesterol-acyl transferase	9 <i>c</i> , 12 <i>t</i> -9 <i>t</i> , 12 <i>c</i> -9 <i>t</i> , 12 <i>t</i> -18:2	24
Cholesteryl ester synthetase	$t$ , $t$ -18:2	25
Cholesteryl hydrolase	$t$ , $t$ - $c$ , $t$ - $t$ , $c$ -18:2	26
Phospholipid acyl transferases	9 <i>c</i> , 12 <i>t</i> -9 <i>t</i> , 12 <i>c</i> /9 <i>t</i> , 12 <i>t</i> -18:2	33
	9 <i>c</i> , 12 <i>t</i> -9 <i>t</i> , 12 <i>c</i> -9 <i>t</i> , 12 <i>t</i> -18:2	34
	2,5 to 14, 17 $c$ , $c$ -18:2	35
	9 <i>t</i> , 12 <i>t</i> -18:2	22
Acyl CoA activation	$t$ , $t$ -18:2	36
Enoyl-CoA isomerase	3 <i>t</i> , 5 <i>t</i> -18:2	37
Arachidonic acid synthesis	9 <i>t</i> , 12 <i>t</i> -9 <i>t</i> , 12 <i>c</i> -9 <i>c</i> , 12 <i>t</i> -18:2	38
Inhibition of 20:3 conversion to PGE <sub>1</sub>	isomers of 20:2/20:3/20:4	39
Prostaglandin synthesis	8 <i>c</i> , 11 <i>c</i> , 14 <i>c</i> -18:3/19:3/21:3/22:3	40
	5 <i>c</i> , 8 <i>c</i> , 11 <i>c</i> , 14 <i>c</i> -19:4/21:4	41
Inhibition of prostaglandin	8 <i>c</i> , 12 <i>t</i> , 14 <i>c</i> -20:3	42
Prostaglandin synthetase	5 <i>c</i> , 8 <i>c</i> , 12 <i>t</i> , 14 <i>c</i> -20:4	43
Arachidonic acid synthesis	$t$ , $t$ -18:2	44
Prostaglandin synthetase	$t$ , $t$ -18:2	45
Elongation	19:3/20:3/21:3/19:4/20:4/21:4/22:4 $\omega$ 3 acids	46
	4,7 to 11, 14 <i>c</i> , $c$ -18:2	47
	4,7,10 to 9,12,15 <i>c</i> , $c$ -18:3	48

monounsaturated fatty acid isomers in commercial salad oil and shortening containing hydrogenated soy oil typically have the double bond in the  $\Delta 8$ - $\Delta 13$  position (2-4). Diunsaturated isomers in these oils contain *cis*, *cis*-; *trans*, *cis*-; and *cis*, *trans*-configurations with the double bond located mainly in the 8,12; 9,12; 9,13; 9,14 and 9,15 positions (5). Trace amounts of conjugated dienes may be present (6).



**FIG. 1.** Orthogonal projects of octadecadienoic acid isomers.

This review is intended to illustrate the variety of recent *in vitro*, *in vivo* and nutritional related studies that have been concerned with the biochemistry and metabolic fate of specific positional and geometrical isomers in hydrogenated soybean oil. The results of many excellent studies with mixture of hydrogenated soybean oil isomers and older references are not included but have been reviewed previously (7-12). The biochemistry and metabolic effects of the longer carbon chain isomers in hydrogenated rapeseed and marine oils have been reviewed by others (13,14).

### General Comments

The synthesis of a large number of pure fatty acid isomers has provided the substrates necessary to investigate a number of the enzymes involved in their biochemistry. Some representative *in vitro* studies are listed in Tables I and II which demonstrate that each isomer is biochemically different and that double bond position can be biochemically at least as important as double bond configuration.

This observation should not be surprising in view of the differences in the physical properties of individual isomers (46-52) and differences in the conformation of the fatty acid chain due to double bond configuration and positions. For example, Figure 1 compares possible conformations of geometrical octadecadienoic acid isomers. Each isomer can exist in a number of configurations but the preferred configuration for enzyme reactions is not known.

Whether or not the results of *in vitro* experiments accurately reflect important reactions or meaningful reaction rates in *in vivo* systems is another question. A degree of caution must be used when interpreting *in vitro* results by themselves, since it is well appreciated that in enzyme-catalyzed reactions, the microenvironment, other cellular constituents and physical interactions can have a major effect on reactions rates and products. Although enzyme studies provide valuable information on the enzyme-fatty acid isomer reactions, the biological significance of these reactions must be confirmed by *in vivo* experiments.

The citations in Table II mainly list studies with the geometric isomers of linoleic acid (particularly 9*t*,12*t*-18:2) and relatively few investigations with positional isomers of polyunsaturated fats. The lack of studies with specific positional octadecadienoic acid isomers and the large number of 9*t*,12*t*-18:2 studies are mainly due to the difference in availability of the isomers. Future nutritional studies with positional 18:2 isomers will be of interest because of the biological importance of linoleic acid and because levels of many of the positional 18:2 isomers in hydrogenated oil are higher than for  $t$ ,  $t$ -18:2.

TABLE III

## Distribution of Positional and Geometric Fatty Acid Isomers in Tissue, Blood and Egg Lipids

Experimental model	Diet or isomer fed	Reference
Rat	<i>t,t</i> - <i>c,t</i> - <i>t,t</i> - <i>c</i> -18:2	53
Rat	Hydrogenated vegetable oil	54-56
Rat	Hydrogenated vegetable oil	57-59
Rat	Hydrogenated vegetable oil	60
Human	Ad libitum	61
Human	Ad libitum	62,63
Human	Ad libitum	64
Human	Ad libitum	65
Swine	Hydrogenated vegetable oil	66
Swine	Hydrogenated vegetable oil	67
Laying hen	$\Delta$ 8-12 <i>c</i> -18:1- <sup>3</sup> H	68
Laying hen	8 <i>t</i> -10 <i>t</i> /12 <i>t</i> -18:1- <sup>3</sup> H	69-71
Human	9 <i>t</i> -12 <i>t</i> -12 <i>c</i> -13 <i>t</i> -13 <i>c</i> -18:1- <sup>2</sup> H	72-75
Rat liver mitochondria	$\Delta$ 5-15 <i>c</i> -18:1	76
Human and rat brain	9 <i>t</i> -18:1/9 <i>t</i> ,12 <i>t</i> -18:2	77
Rat placenta and fetus	9 <i>t</i> -18:1- <sup>14</sup> C/9 <i>t</i> ,12 <i>t</i> -18:2- <sup>14</sup> C	78
Dog and rat	9 <i>t</i> -18:1/9 <i>t</i> ,12 <i>t</i> -18:2	79

A number of representative studies on the distribution of positional octadecenoic acid and geometrical octadecadecenoic acid isomers into tissue lipids are cited in Table III (53-79). These studies have used both pure (labeled and nonlabeled) unsaturated isomers and hydrogenated vegetable oils containing mixtures of isomers and a variety of organisms and experimental designs. Nutritional and physiological effects of individual fatty acid isomers and hydrogenated vegetable oils have been the subject of a large variety of experimental protocols. The references cited in Table IV illustrate some of the many parameters investigated. The combination of results from both *in vitro* studies (Table I an II) and from *in vivo* studies (Tables III and IV) are summarized in these tables and provide an opportunity to assess the relative importance of enzyme selectivities on biochemical reactions in whole organism experiments.

## ABSORPTION OF ISOMERIC FATS

Ingested triglycerides (TG) undergo a series of reactions that begin with hydrolysis by pancreatic lipase. About 96% of the dietary TG are absorbed as free fatty acids, mono-

TABLE IV

Effects of Fatty Acid Isomers *in vivo*

Experimental model	Diet or isomer	Parameter investigated	Reference
Cultured rat myocytes	9 <i>t</i> -18:1 and <i>t,t</i> -18:2	Arrhythmia susceptibility	80
Rats	<i>t,t</i> -18:2	Tissue prostaglandin levels	81
Rats	<i>t,t</i> -18:2	Kidney lipids	82
Rats	<i>t,t</i> -18:2	Lung lipids	83
Rats	18:2 isomers	Linoleic acid metabolism	53
Rats	<i>t,t</i> -18:2	Lipoproteins	84
Rats	<i>t,t</i> -18:2	Platelet aggregation	85
Rats	18:2 isomers	Developing brain	86
Rats	9 <i>t</i> -18:1	Weight, skin permeability, lipid composition	6
Rats	<i>t,t</i> -18:1	Blood coagulation	87
Rats	Hydrogenated soy oil	LCAT activity	88
Microorganisms	$\Delta$ 2-17 <i>c</i> -18:1 isomers	Cell growth	89
<i>Escherichia coli</i> mutant	$\Delta$ 3-15 <i>t</i> -18:1 isomers	Cell growth	90
<i>Escherichia coli</i> mutant	9 <i>t</i> -11 <i>c</i> -11 <i>t</i> -18:1	Cyclic AMP requirements	91
<i>Saccharomyces cerevisia</i>	9 <i>t</i> - and 11 <i>t</i> -18:1	Cell division and lipid synthesis	92
Rats	Hydrogenated soy oil	EFA requirements	93
Rats and dogs	9 <i>t</i> -18:1 and 9 <i>t</i> ,12 <i>t</i> -18:2	Oxidation rates and turnover	79
Rats	<i>trans</i> isomers + safflower oil	Growth and enzyme activity	94
Mice	Hydrogenated soy oil	Long-term effects	95,96
Rats	Hydrogenated vegetable oil	Long-term effects	97
Rats	<i>t,t</i> -18:2	Growth, organ weight	98
Rats	<i>trans</i> 18:1 and 18:2 isomers	$\Delta$ 6 and $\Delta$ 7 desaturase activity	99
Rabbits and monkeys	Hydrogenated soy oil	Hypercholesterolemia and atherosclerosis	100
Swine	Hydrogenated soy oil	Lipoprotein	67
Swine	Hydrogenated soy oil	Atherosclerosis	66
Swine	Hydrogenated soy oil	Atherosclerosis	101
Humans	Hydrogenated soy oil	Serum cholesterol	102
Humans	Hydrogenated vegetable oil	Serum cholesterol	103
Rabbits	Hydrogenated vegetable oil	Atherosclerosis	104
Mice	Hydrogenated vegetable oil	Tumors	105
Rats	Hydrogenated vegetable oil	Prostaglandin levels	106
Rabbits	Hydrogenated olive oil	Fatty acid composition	107
Human	9 <i>t</i> -18:1/12 <i>t</i> -18:1/12 <i>c</i> -18:1	Fatty acid composition	108
Human	13 <i>t</i> -18:1/13 <i>c</i> -18:1	Fatty acid composition	75
Rat heart	Hydrogenated fat	Oxygen uptake	109

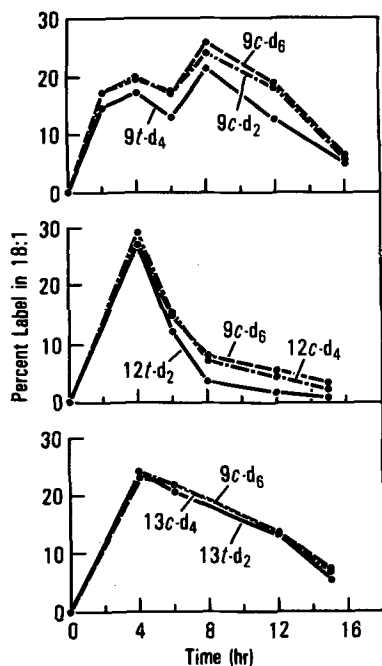


FIG. 2. Incorporation of deuterium labeled *cis*-9-, *trans*-9-, *cis*-12-, *trans*-12-, *cis*-13-, and *trans*-13- octadecenoic acids into human chylomicron triglycerides (72-75).

and diglycerides by the intestinal mucosa membrane, where they are largely reesterified to TG and to a lesser degree to phospholipids and cholesteryl esters. Packaging of the TG into chylomicrons then occurs, followed by transport via the lymphatic system to the circulatory system. A small percentage of the TG is also transported directly to the liver via the portal vein.

The effect of double bond position on *in vitro* hydrolysis of a series of TG containing *cis* positional 18:1 isomers by pancreatic lipase has been reported (15). A double bond in the  $\Delta 2$ - $\Delta 7$  positions significantly inhibited TG hydrolysis. However, little inhibition of lipase activity was found for TG substrates containing the  $\Delta 8$  to  $\Delta 16$  *c*-18:1 acids. Based on these results, one would expect hydrogenated fats to be well absorbed since they contain the  $\Delta 8$  to  $\Delta 15$ -18:1 isomers. Similar data for a series of TG containing the *trans* positional 18:1 isomers are not available.

Human studies using mixtures of TG containing deuterium labeled 9*t*-, 12*c*-, 12*t*-, 13*c*-, 13*t*-18:1 isomers (Fig. 2) show no discrimination for absorption relative to deuterated 9*c*-18:1 even though the absorption pattern varies considerably from subject to subject and there is a wide variation in melting points for these isomers (72-75). Analysis of human adipose tissue total lipids (Fig. 3) indicates that all the 18:1 positional isomers are present at about the levels expected, based on estimated dietary intake (62,63). Since adipose tissue is considered to be a good reflection of dietary fat intake, these data imply that all the 18:1 isomers in hydrogenated vegetable oils are well absorbed. Similar data for the polyunsaturated fatty acid isomers have not been reported, but based on the 18:1 data no problems with absorption of the 18:2 isomers should be expected.

Once the chylomicrons enter the circulatory system, a number of biochemical transformations catalyzed by a large variety of enzymes occur. The metabolic fate of a major portion of dietary fats is catabolism to CO<sub>2</sub> and H<sub>2</sub>O via

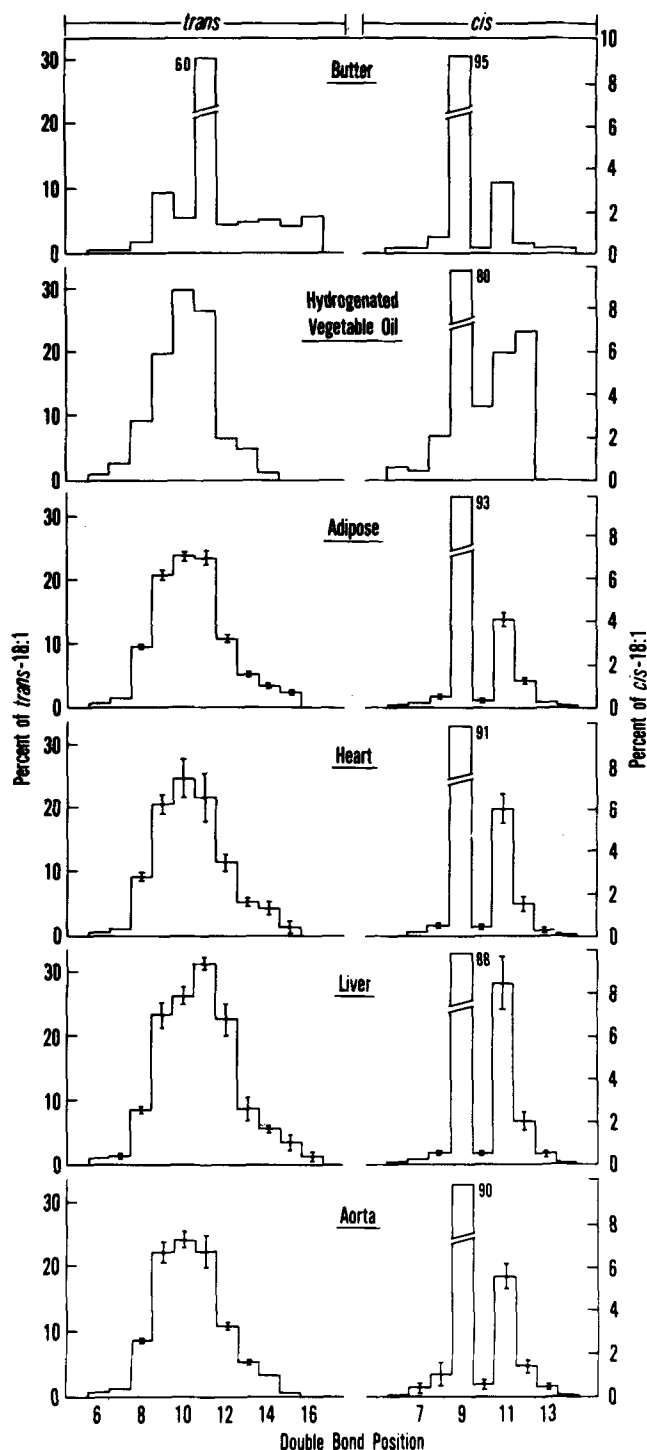


FIG. 3. Distribution of positional *cis*- and *trans*-octadecenoic acid isomers in human tissue total lipids compared to isomer distribution in butter and hydrogenated vegetable oil (62).

$\beta$ -oxidation. The first step in  $\beta$ -oxidation of fatty acids and in many other lipid enzyme reactions is activation by CoA ester formation via CoA synthetase. The rates for CoA ester formation for a series of  $\Delta 4$  to  $\Delta 16$  *cis* and *trans* positional octadecenoic acids were determined (16,17). Reaction rates for each *trans* positional isomer was higher than its corresponding *cis* positional isomer. The rates of acyl CoA ester formation were the lowest for those isomers with the double bond near the center ( $\Delta 8$  to  $\Delta 10$ ) of the fatty acid chain. Within the series of *trans* positional isomers, the even-

## BIOCHEMISTRY OF FATTY ACID ISOMERS

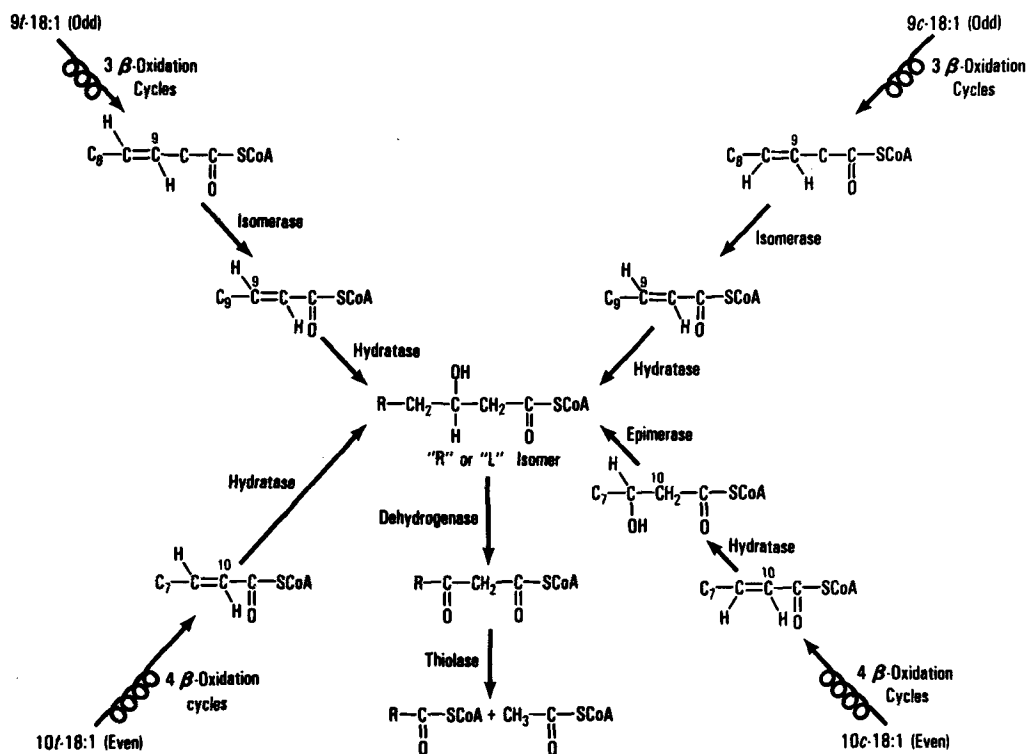


FIG. 4.  $\beta$ -Oxidation of *cis*- and *trans*-octadecenoic acid positional isomers containing double bonds in the odd- and even-numbered positions.

numbered isomers had higher rates than adjacent odd-numbered isomers. Reaction rates for the series of *cis* positional isomers produced the opposite pattern, with the odd-numbered isomers having the higher rates. The results were variable, depending on the temperature, pH, fatty acid concentration and detergents used in the incubation medium. This sensitivity to *in vitro* experimental conditions suggests that *in vivo* rates may be quite different.

### $\beta$ -OXIDATION

After a fatty acid is activated by formation of the CoA ester,  $\beta$ -oxidation proceeds through several  $\beta$ -oxidation cycles until a double bond is reached. At this point (see Fig. 4) a  $\Delta^3$ - $\Delta^2$  enoyl-CoA isomerase (37) is required to conjugate the double bond if the double bond in the fatty acid isomer was originally in an odd-numbered position. The substrate for the enoyl-CoA isomerase is either a *cis* or *trans* double bond, depending on the configuration of the original fatty acid isomer, which may influence the overall oxidation rate. In the case of positional fatty acid isomers, a 3-hydroxy acyl-CoA epimerase is required to convert the D-3-hydroxy isomer produced by oxidation of even (*cis*-18:1) isomers to the L-3-hydroxy isomer. The remainder of the  $\beta$ -oxidation steps are then similar for both "even" and "odd" unsaturated isomers.

*In vitro* oxidation of *cis*-octadecenoate CoA esters positional isomers by rat liver and heart mitochondria preparations indicates that *cis*-18:1 isomers with even-numbered double bonds were oxidized more slowly than the immediate adjacent odd-numbered *cis*-18:1 isomer (18). Most *trans*-18:1 isomers with even-numbered double bonds were oxidized by rat liver mitochondria more rapidly than adjacent odd-numbered *trans*-18:1 isomers. Generally, *trans*-18:1

isomers were also oxidized slightly more slowly than their respective *cis* isomer (Fig. 5).

Various explanations that have been offered to explain these different *in vitro*  $\beta$ -oxidation rates include slower rates for CoA activation, lower enoyl-CoA isomerase activity for the *trans*-3 double bond, and lower transfer rates through cell membranes as the rate-controlling step responsible for fatty acid isomer  $\beta$ -oxidation rates.

Analysis of human tissues (see Fig. 3) after long-term ingestion of hydrogenated oils (62,63) indicates that no significant accumulation or discrimination of any specific *cis*- or *trans*-18:1 positional isomer occurs, with the exception

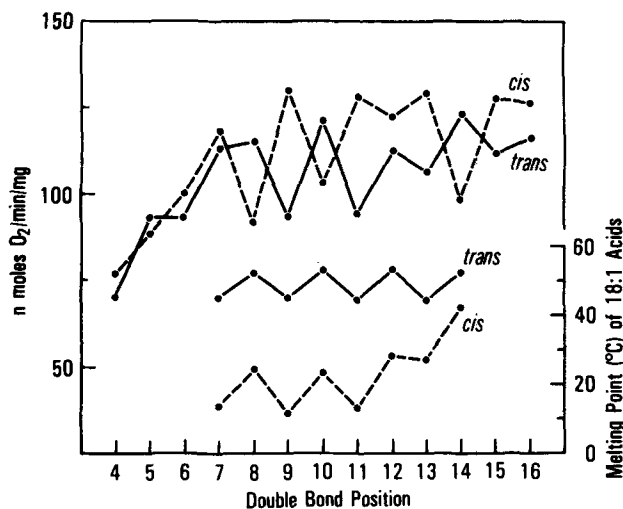


FIG. 5.  $\beta$ -Oxidation rates for positional isomers of *cis*- and *trans*-octadecenoate CoA esters by rat liver mitochondria (18) and melting points of octadecenoic fatty acid isomers.

TABLE V

Selectivity Values for Incorporation of 18:1 Isomers into the 1- and 2-Acyl Positions of Phosphatidylcholine (72-75)

Isomer	Selectivity value <sup>a</sup>		
	Total PC	1-acyl PC	2-acyl PC
9 <i>t</i> -18:1	+0.02	+0.56	-0.21
12 <i>t</i> -18:1	+0.17	+0.73	-0.90
12 <i>c</i> -18:1	+0.58	+0.51	+0.65
13 <i>t</i> -18:1	-0.03	+0.70	-0.95
13 <i>c</i> -18:1	-0.06	+0.43	-0.22

<sup>a</sup>Average for data from 2 subjects.

that in liver 11*t*-18:1 rather than 10*t*-18:1 is the most prevalent isomer. Fatty acid with the double bond towards terminal methyl were found in slightly higher levels than expected based on hydrogenated oil composition. Correlation of the fatty acid pattern in human tissue suggests that 90-95% of the monoene isomers are from hydrogenated oil (63). Relative turnover rates of labeled fatty acid isomers compared to 9*c*-18:1 in short-term human experiments (72-75) also generally indicate no significantly slower or more rapid clearance of the 18:1 isomers from plasma with the possible exception of 12*c*-18:1. The combined data suggest that in vitro factors which influence  $\beta$ -oxidation may be significantly modified in vivo. Rats fed *t,t*-, *c,t*- and *t,c*-18:2 isomers were found to deposit *t,t*-18:2 and *t,c*-18:2 into liver lipids at levels expected, based on dietary content, but only low levels of *c,t*-18:2 were deposited (53). Lack of excessive accumulation in liver and adipose tissue implies  $\beta$ -

oxidation is not inhibited, but the level of arachidonic acid was decreased by high levels of *t,t*-18:2 and was not influenced by *t,c*- or *c,t*-18:2.

## ENZYMATIC SELECTIVITY

There is considerable in vivo and in vitro evidence for selective recognition of double bond position and configuration by a variety of enzymes that are responsible for incorporation of fatty acids into specific lipid classes.

In vitro reaction rates for incorporation of *cis*- and *trans*-18:1 positional isomers into the 1- and 2-acyl positions of phosphatidylcholine by rat liver microsomes illustrate the influence of double bond position and configuration on the phosphatidylcholine acyl transferase reaction (20,21). In general, acylation of 2-acyl phosphatidylcholine by the 7-, 9-, 11- and 13-*cis*-18:1 isomers were 3 to 5-fold lower than the rates for the 8-, 10- and 12-*cis*-18:1 isomers. Acylation of 2-acyl phosphatidylcholine with the 6-, 8-, 9-, 11-, 13- and 15-*trans*-18:1 isomers were ca. 0.5-3 times higher than the 7-, 10-, 12- and 14-*trans*-18:1 isomers. A similar even-odd pattern for acylation of 1-acyl phosphatidylcholine with a series of *cis* and *trans*-18:1 positional isomers was not found. The acylation rates for the 2-position were also generally much lower than the rates for the 1-position. Within the *cis* series, the highest rates for the 2-acyl position were found for the 9-, 12- and 13-positional isomers. The 2-acyl phosphatidylcholine acylation rate for the 9*t*-18:1 isomer was roughly twice the rate for the other *trans*-18:1 positional isomers. The sensitivity of acyl transferase specificities to both double bond configuration and posi-

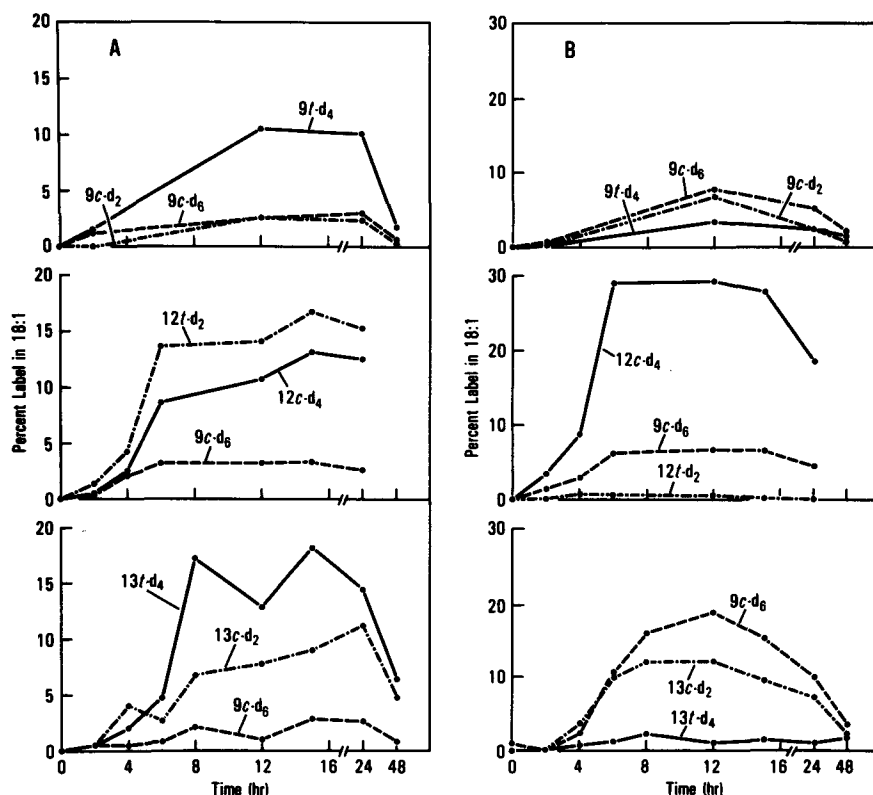


FIG. 6. Distribution of deuterium labeled *cis*,9-; *trans*,9-; *cis*,12-; *trans*,12-; *cis*,13-; and *trans*,13-octadecenoic acids into the 1-acyl (A) and 2-acyl (B) positions of phosphatidylcholine from human plasma samples (72-75).

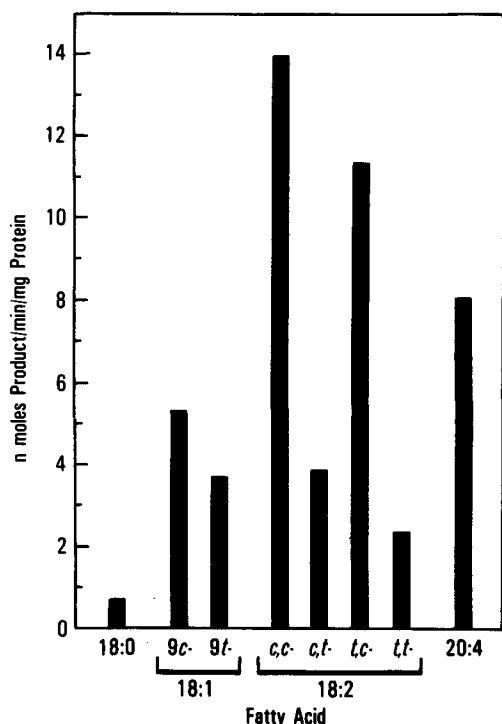


FIG. 7. Acyl transferase specificities for incorporation of *trans,trans*-, *cis,trans*-, *trans,cis*-, and *cis,cis*-9,12-octadecadienoic acids into the 2-acyl position of phosphatidylcholine (34).

tion are qualitatively supported by in vivo human plasma-PC data for five 18:1 isomers (Table V) (72-75). Quantitatively there is a large difference between the 2-acyl PC rat liver microsomes data for the 12*c*-18:1 isomer and the human plasma results in Table V and in Figure 6.

Acyl transferase specificities for incorporation of *t,t*-

*c,t*-, *t,c*- and *c,c*-18:2 into the 2-acyl position of phosphatidylcholine are compared to 18:0, 9*c*-18:1 and 9*t*-18:1 in Figure 7 (34). The difference in the reaction rates for *c,t*- and *t,c*-18:2 is striking. These data are consistent with the low incorporation of *c,t*-18:2 relative to *t,c*-18:2 into rat liver phospholipids (53) and, when combined with the 12*t*- and 12*c*-18:1 human plasma data (74), suggest that the specific position and configuration of the *cis*,12- double bond has considerable biological importance.

Acyl CoA:phospholipid acyl transferase reaction rates for 1-acyl and 2-acyl phosphatidylcholine and phosphatidylethanolamine with a series of methylene-interrupted *cis,cis*-octadecadienoate CoA esters are plotted in Figure 8 (35). The relatively high rates for acylation of the 2-acyl PC and PE positions with 9*c*,12*c*-18:2 are expected, considering the biological importance of this fatty acid. The acyl transferase rates for the octadecadienoic acids containing a 1,4-pentadiene system in the omega end of the acyl chain are higher than might be expected, since organisms have had no reason to develop an efficient mechanism for incorporation of positional octadecadienoic acid isomers that normally are not present in their dietary fats.

Both in vitro and in vivo data indicate that cholesteryl esterase and phosphatidylcholine:cholesterol acyl transferase are also very sensitive to double bond configuration and position (24-26). The incorporation of fatty acid isomers relative to 9*c*-18:1 into human plasma cholesteryl ester fractions shown in Figure 9, displays a moderate to nearly absolute discrimination against the various isomers (72-75). Comparisons of CE selectivity values to other human plasma lipid selectivity values are summarized in Figure 10. In contrast to the lecithin:cholesterol acyl transferase (LCAT) specificities, cholesteryl hydrolase specificities (27) for cholesteryl *cis*-octadecenoate esters appear less sensitive to double bond position. The maximum hydroly-

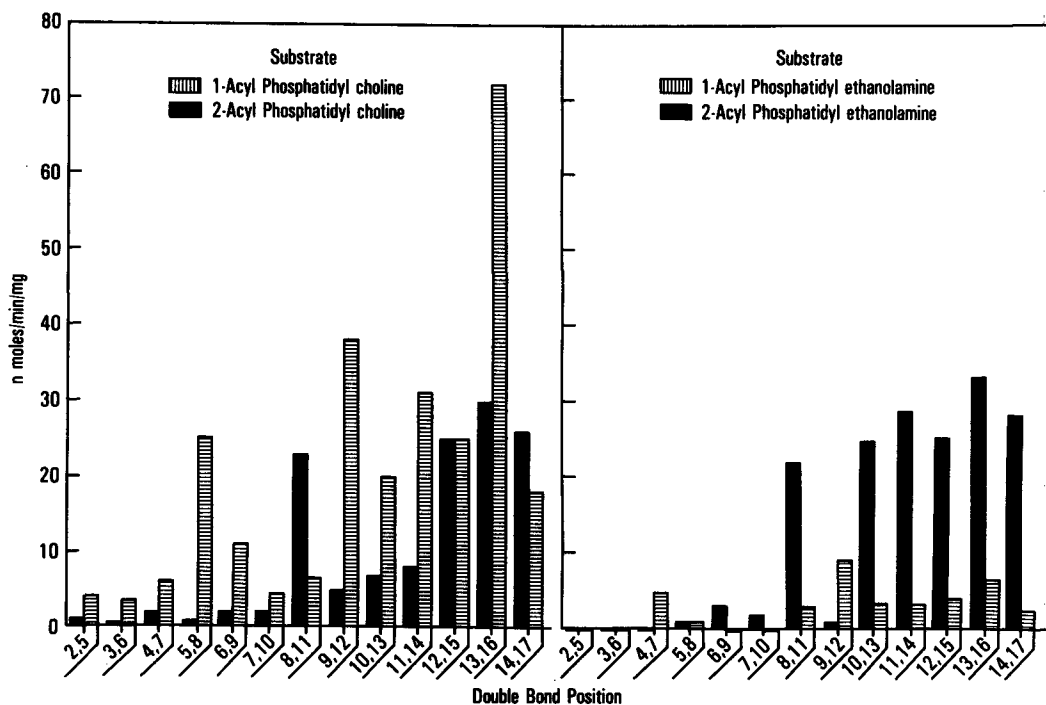


FIG. 8. Acyl transferase activities of rat liver microsomes for acylation of 1-acyl and 2-acyl phosphatidylcholine (PC-1 and PC-2) and 1-acyl and 2-acyl phosphatidylethanolamine (PE-1 and PE-2) with a series of *cis,cis*-octadecadienoate CoA esters (35).

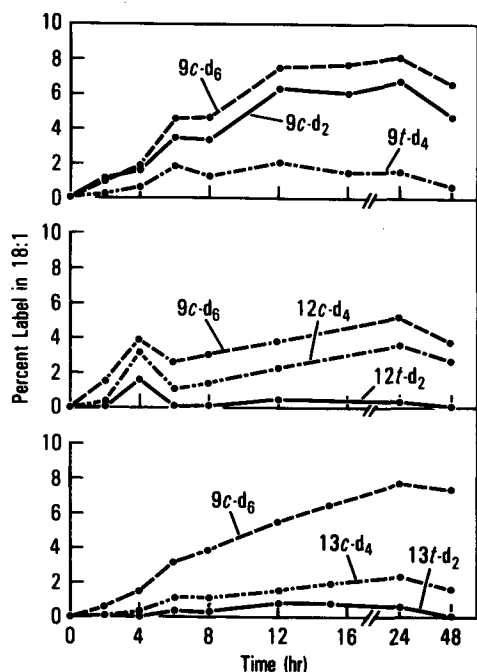


FIG. 9. Distribution of deuterium labeled *cis*-9-, *trans*-9-, *cis*-12-, *trans*-12-, *cis*-13-, and *trans*-13-octadecenoic acids in human plasma cholesteryl ester samples (72-75).

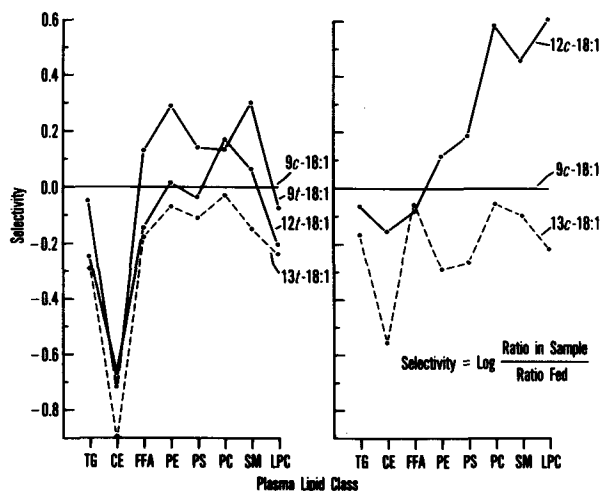


FIG. 10. Selectivity values for incorporation of deuterium labeled *trans*-9-, *trans*-12-, *trans*-13-, *cis*-12- and *cis*-13-octadecenoic acids into human plasma lipid classes (72-75).

sis rate occurs for the *9c*-18:1 cholesteryl ester and gradually decreases as the double bond position is moved towards the carboxyl and omega ends of the fatty acid chain. Similar data for cholesteryl esters containing *trans*-octadecenoic and octadecadienoic acid isomers have not been reported.

The presence of long chain ( $C_{20}$ - $C_{24}$ ) unsaturated fatty acids in mammalian tissue is derived in part from elongation and desaturation of  $C_{18}$  dietary fats. Both elongation and desaturation of a series of positional *cis*- and *trans*-octadecenoic acids have been reported with *in vitro* systems (28-32). Based on whole organism experiments, these conversions appear to be of relatively minor importance. Rat, laying hen and human experiments with various labeled 18:1 isomers generally have failed to detect desaturated or elongated products when adequate levels of linoleic acid are present

TABLE VI

Inhibition of  $PGE_1$  Biosynthesis from *8c*,*11c*,*14c*-20:3 (39)

	Fatty acid added	Relative rate of $PGE_1$ synthesis
all- <i>cis</i>	<i>8c</i> , <i>11c</i> -20:2	100
	<i>8c</i> , <i>14c</i> -20:2	75
	<i>11c</i> , <i>14c</i> -20:2	75
	<i>8c</i> , <i>11c</i> , <i>14c</i> -18:3	45
	<i>9c</i> , <i>12c</i> , <i>15c</i> -18:3	70
mono- <i>trans</i>	<i>8c</i> , <i>11c</i> , <i>14c</i> -19:3	95
	<i>8c</i> , <i>11c</i> , <i>14c</i> -22:3	95
	<i>5c</i> , <i>8c</i> , <i>11c</i> , <i>14c</i> , <i>17c</i> -20:5	45
	<i>8c</i> , <i>11t</i> , <i>14c</i> -20:3	100
	<i>8c</i> , <i>11c</i> , <i>14t</i> -20:3 + <i>8t</i> , <i>11c</i> , <i>14c</i> -20:3 (1:1)	90
mono-conjugated	<i>5c</i> , <i>8c</i> , <i>11c</i> , <i>14t</i> -20:4	70
	<i>2t</i> , <i>8c</i> , <i>11c</i> , <i>14c</i> -20:4	95
	<i>8c</i> , <i>10t</i> -20:2 + <i>9t</i> , <i>11c</i> -20:2 (1:1)	65
	<i>11c</i> , <i>13t</i> -20:2 + <i>12t</i> , <i>14c</i> -20:2 (55:45)	60
	<i>8c</i> , <i>10t</i> , <i>14c</i> -20:3 + <i>8c</i> , <i>12t</i> , <i>14c</i> -20:3 (1:1)	2

in the diet. The exception appears to be the *10t*-18:1 isomer, which is desaturated to a conjugated octadecadienoic acid in the laying hen (71).

Reaction rates for elongation of all *cis* methylene-interrupted octadecadienoic and six octadecatrienoic positional isomers by rat liver microsomes has been reported (45). The *6c*,*9c*- and *7c*,*10c*-18:2 isomers were elongated at much higher rate than the other isomers, including *9c*,*12c*-18:2. The *5c*,*8c*,*11c*-; *6c*,*9c*,*12c*- and *7c*,*10c*,*13c*-18:3 were also elongated 5-10 times more rapidly than *9c*,*12c*,*15c*-18:3. These results are of interest because of the possible physiological impact of dietary  $\omega$ 3 fatty acids on platelet aggregation and their implied role as prostaglandin precursors.

## PROSTAGLANDIN SYNTHESIS

The question of whether isomeric fatty acids are inhibitors of prostaglandin synthesis or if they are converted to biologically active prostaglandin isomers is of general concern. In spite of the extensive literature on prostaglandins, this question is basically unanswered. Several polyunsaturated isomers listed in Table VI have been tested as inhibitors for the conversion of *8c*,*11c*,*14c*-20:3 to  $PGE_1$  by the particulate fraction from sheep vesicals (39,41). A number of these fatty acids were found to inhibit  $PGE_1$  synthesis, with a conjugated mono-*trans* isomer (*8c*,*12t*,*14c*-20:3) producing almost complete inhibition of  $PGE_1$  synthesis.

Conversion of various carbon chain length polyunsaturated fatty acids containing the basic *8c*,*11c*,*14c*- double bond structure to biologically active prostaglandins has been reported (39,40,44). Whether these reactions would occur to any significant extent *in vivo* where adequate levels of the normal 20:3 and 20:4 prostaglandin precursors are present is unknown. Hydrogenated vegetable oil and *9t*,*12t*-18:2 fed to rats have been found to reduce the levels of tissue prostaglandins (81,106). The physiological effects of these observations are still speculative.

## EFFECTS OF FATTY ACID ISOMERS

A number of studies with fatty acid isomers listed in Table



IV illustrate the variety of nutritional and physiological effects that have been investigated. The references cited are generally from recent studies plus a sampling of older papers. In contrast to the many enzymatic studies listed in Tables I and II, which were concerned with a variety of specific positional and geometric isomers, the studies in Table IV have generally been limited to hydrogenated oils or 9*t*,12*t*-18:2 and 9*t*-18:1 isomers because these isomers have been the only ones readily available in reasonable quantities. Unfortunately, data for the 9*t*,12*t*-18:2 isomer does not facilitate the interpretation of results with hydrogenated vegetable oils because commercially hydrogenated oils contain little or no 9*t*,12*t*-18:2.

A few of the many studies that have investigated the effect of hydrogenated vegetable oils on atherosclerosis, serum cholesterol, and triglyceride levels are listed in Table IV. These studies utilized experimental and control diets that were well matched in terms of their total saturated/monounsaturated/polyunsaturated fatty acid ratios and investigated two or more levels of *trans* fatty acids. In the human experiments (102,103), the results indicated no physiologically significant effect on serum cholesterol or triglycerides levels, and the results from animal studies did not find an increase in the number of arterial lesions or development of atherosclerosis (66,100,101,104).

In spite of the wide difference in melting points and the wide range in reaction rates for the various isomeric fatty acids, physiologically significant effects have not been reported for animal or human studies with hydrogenated fats where extenuating experimental factors such as low linoleic acid levels or large differences in total fat intake were not involved. Applewhite (11) has recently reviewed the influence of low linoleic acid levels in studies with hydrogenated soybean oil. A reasonable explanation for the lack of significant effects is that the normal fatty acids (i.e., stearic, palmitic, oleic, linoleic, etc.), which mammalian organisms regularly metabolize, have as wide a variation in melting points, structures, enzyme specificity and reaction rates as do isomeric fatty acids. In general, humans must be able to accommodate a wide change in the composition of fatty acids, depending on whether the diet contains fats from fish, vegetable or animal sources. Without this obvious ability to adequately metabolize a variety of fats with different physical structures and biological properties, we probably could not tolerate our present diet as well as we do. It is accepted that, at least for a percentage of the population, the quantity and type of fat consumed can have an impact on the development of atherosclerosis. This point suggests that for sensitive individuals, specific fats may induce a biological or metabolic overload. The contribution of high saturated fat diets to the development of hyperlipidemia and the studies on erucic acid are familiar examples.

Biochemical and physiological research on isomeric fatty acids in hydrogenated oils have substantially increased our understanding of lipid metabolism. However, with this greater understanding has come the realization that lipid metabolism is an exceedingly complex problem, and there is no consensus of opinion on the role of isomeric fats in nutrition and health. By appropriate selection of published data, either a positive or a negative argument can be developed for the nutritional value of hydrogenated vegetable oils.

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