The biosynthesis and oxidation of branched and cyclopropane fatty acids of normal structure with an odd number of carbon atoms

by E.K. Alimova, and A.T. Astbatsatur'yan

Original title: Biosintez i okislenie zhirnykh kislot normal'nogo stroeniya s nechetnym chislom atomov C, razvetvlennykh i tsiklopropanovykh

From: Uspekhi sovremennoi biologii (Achievements of Modern Biology), 76(1) : 34-53, 1973

Translated by the Translation Bureau (LHM) Multilingual Services Division Department of the Secretary of State of Canada

Department of the Environment Fisheries and Marine Service
Halifax Laboratory
Halifax, N.S.
1974

36 pages typescript
**Author** - E. K. Alimova and A. T. Astbatsatur'yan

**Title in English** - The biosynthesis and oxidation of branched and cyclopropane fatty acids of normal structure with an odd number of carbon atoms

**Title in Foreign Language** - Biosintez i okislenie zhirnykh kislot normal'nogo stroeniya s nechetnym chislom atomov C, razvetvlennykh i tsiklopropanovykh

**Reference in Foreign Language** - Uspekhi sovremennoi biologii

**Reference in English** - Achievements of Modern Biology

**Publisher** - Not given

**Place of Publication** - USSR

<table>
<thead>
<tr>
<th>Year</th>
<th>Volume</th>
<th>Issue No.</th>
<th>Number of Typed Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>76</td>
<td>1</td>
<td>36</td>
</tr>
</tbody>
</table>

**Requesting Department** - Environment

**Branch or Division** - Office of the Editor, Fisheries Services

**Person Requesting** - Dr. Ackman

**Date of Request** - March 27, 1974

UDC 655.12/542.91

The biosynthesis and oxidation of branched and cyclopropane fatty acids of normal structure with an odd number of carbon atoms

By E.K. Alimova and A.T. Astbatsatur'yan, Rostov-on-Don.

This article summarizes present-day knowledge of the distribution, quantitative content in various organisms and biosynthesis and oxidation mechanisms of the higher fatty acids of normal structure (both branched and with propane cycles) with uneven numbers of carbon atoms. Data obtained in experiments on animal and plant tissues, bacteria and yeasts is also taken into consideration. Alternate ways of de novo biosynthesis of fatty acids are evaluated; it is shown that their biosynthesis is a function of the accessibility of corresponding substrata. Alternative ways of oxidation of fatty acids, both branched and with an uneven number of carbon atoms — α and β-oxidation, and alternating α-β-oxidation in micro- and macro-organisms — are evaluated.

Higher fatty acids, both those of normal structure with an uneven number of carbon atoms (FA_{unev}) and also those that are branched (FA_{br}) with an even or uneven number of carbon atoms, are found in all organisms: bacteria, fungi, plants, tissues of animals and man, and food products of animal

* Numbers in the right-hand margin indicate the corresponding page numbers in the original.
origin. In some lipid fractions in various animal and human tissues, they accumulate in quite significant quantities. Thus, in the lipids of dog hair, single-branched C₁₅ - acid has been recorded in the quantity of 12% (of the total amount of acids), while the skin lipids contained more than 70% branched C₁₈ - acid (out of the total quantity of C₁₈ - acids) (Wheatley and Sher, 1961). In the cholesterol esters of the lipids of a dog's lung, C₁₅:₀ - and C₁₇:₀ - acids make up 28 mol.% out of 79 mol.% of all saturated acids (Morgan et al., 1965). Noticeable quantities of C₁₇:₀ - acid have been discovered in various fractions of plasma lipids, and C₁₅:₀ - and C₁₇:₀ - acids have been found in the bile lipids of rats (Blomstrand and Larsson, 1962). FA unev have also been detected in the human organism: in red blood cell lipids they amount to 6.1%; in those of the spleen, 3.9-4.8%; in the placenta, 2.7%; in the liver, 7.4-10.8%; in the lungs, 4.8%; and in the kidneys, 4.7-6.3% (in percentages relative to total content of fatty acids). Long-chained C₁₇:₀, C₁₉:₀, C₂₁:₀, C₂₃:₁ and C₂₅:₁ - acids are concentrated mainly in the sphingomyelins of the blood plasma - at the rate of 6.1% (Svennerholm et al., 1966). In the lipids of whole blood, C₁₅:₀ and C₁₇:₀ - acids make up 10.6% of saturated acids (Glaser et al., 1962).

Saturated and unsaturated FA unev ranging from C₇ to C₂₃ have been found in all lipid fractions in human hair (Singh and Gershbein, 1967), while others ranging from C₇ to C₂₅ with normal chains and from C₈ to C₂₅ branched, and a C₁₅ with multiple branches have been discovered in the lipids of human skin (Downing, 1963; Wheatley and Fiesch, 1967; Carruthers, 1964; Hahti and Horning, 1964; Nicolaides et al., 1964; Nicolaides, 1965 and 1967; Nicolaides and Ansari, 1969; Khasina, 1968; and Alimova et al., 1969a). In human skin lipids, FA unev can comprise from 6% (Coon et al., 1963) to 19%
(Kellum, 1967) in relation to total fatty acids, and 10% (James and Wheatley, 1956) in relation to non-esterified fatty acids. According to Downing's data (1963), the quantity of saturated and unsaturated fatty acids in the lipids of the dermal fat of new-born babies is roughly uniform, with $F_{A_{br}}$ composing 78% of saturated $C_{12} \sim C_{30}$ - acids and 79% of unsaturated $C_{10} \sim C_{30}$ - acids. The acids $a-C_{15}$ and $a-C_{17}$ are present in appreciable quantities in lamb fat, as is $a-C_{15}$ in beef fat (Hansen et al., 1952 and 1954).

In the perinephric fat of bulls and sheep, the plasma of cows, the fat in milk, herring and creamery butter (Ackman and Hansen, 1967), and in many human organs (Kremer, 1965), 3, 7, 11 and 15- tetramethylhexadecanoic (phytic) and 2, 6, 10 and 14- tetramethylpentadecanoic (pristanic) acids have been found. In addition, the L- and D,D- isomers of these acids have been found in herring fat, and mixtures of D,D,D- isomers have been found in creamery butter.

In sea mammal oil, $F_{A_{unev}}$ ($C_{15}$, $C_{17}$ and $C_{21}$) are usually found to constitute from 1% to 4% of the total amount of acids (Ackman, 1965). An unusually high content (29%) of saturated, mono- and polyunsaturated $F_{A_{unev}}$ has been found in the oil of Mugil cephalus (Reiser et al., 1963; Gruger et al., 1964; Sen and Schlenk, 1964) and Arenicola marina (Cocker et al., 1963).

The $F_{A_{unev}}$ are very widely represented in microorganisms. According to the data of Saito and Asada (1967), $C_{15}$ and $C_{17}$ $F_{A_{br}}$, which are totally absent from the lipids of the surface of human skin, were discovered in

---

1 Henceforth the prefixes $a-$ (anteiso) and $i-$ (iso) are used in designating fatty acids.
quantities of 58.8% and 23.7% respectively in the lipids of bacteria continually present in the skin. They account for 10% of non-esterified fatty acids and 40-50% of the triglycerides that make up 1/3 - 1/2 of all the lipids of these bacteria. Among the fatty acids in bacteria in the rumens of great horned cattle, FA_{br} in a C_{13} - C_{20} series and phytic acid have been found; with C_{15} making up 16% of them (Hansen, 1966). The lipids of Halobacterium cutirubrum contain mainly the D,D,D isomer of phytic acid with a 5% admixture of the D,D,D isomer of pristanic acid (Ackman and Hansen, 1967). In the non-esterified fatty acids fraction of the free lipids of Pasteurella pestis (vaccenic strain), C_{17}-acid content amounts to 12.8%; in the fatty acids of glycerides it makes up from 12.3 to 22.8%, and in those of the phospholipids, 11.5%. Among the fatty acids of the combined lipids, C_{13:0} accounts for 18.5%, C_{19:0}, 16.3%; C_{17:2}, 2.0%; and C_{17:1}, 1.2% (Alimova and Boikova, 1967). FA_{unev} have been found in noticeable quantities in the lipids of cholera bacilli (vaccenic strain) (Astbatsatur'yan, 1962, 1964; Alimova, 1967) and pseudotubercular bacteria (Astbatsatur'yan, 1962, 1964). A considerable content of iso- and anteiso-fatty acids with uneven and even numbers of carbon atoms has been revealed in the lipids of various species of Bacillus (Akashi and Saito, 1960; Allison et al., 1962; Kaneda, 1963, 1967, 1971; Kates, 1964). In the lipids of B. thuringiensis and B. anthracis, iso-acids (C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17} and C_{17:1}) and anteiso-acids (C_{13}, C_{15} and C_{17}) make up more than 70% of the total acid content (Kaneda, 1968). Of these, i-C_{15} is the most plentiful acid. In the lipids of thermophilic and mesophilic bacilli, FA_{br} with an uneven number of carbon atoms (i- and a-C_{15} and i- and a-C_{17}) predominate (Daron, 1970; Shen et al., 1970). 12-methyltetradecanoic
acids has been discovered in significant quantities in sarcina lipids (Akashi and Saito, 1960). Branched C$_{15}$ acids in amounts ranging from 24% to 49%, with a-C$_{15}$ predominating, have been discovered in the lipids of 22 strains of Corynebacterium acnes (Moss et al., 1967; Moss and Cherry, 1968). A large amount of a-C$_{15}$ acid has been discovered in Propionibacterium acnes, P. freudenreichii and P. shermanii (Moss and Cherry, 1968; Moss et al., 1969). C$_{15}$ and C$_{17}$ acids of various structures have been detected in the lipids of the yeasts Debaryomyces hansenii (Merdinger and Devine, 1965), Candida lipolytica and Rhodotorula glutinis (Kates and Baxter, 1962).

Multi-branched long-chain fatty acids are characteristic of the lipids of mycobacteria (C$_{27}$-phthienoic, C$_{32}$-mycocerosic and C$_{38}$-mycolic acids) and corynebacteria (C$_{32}$ – C$_{34}$ corynomycolic acids). A multibranched acid with a lateral methyl group in its middle links — C$_{18}$-tuberculostearic acid — has been discovered in the lipids of tuberculosis bacteria (Asselineau and Lederer, 1960).

Fatty acids with a propanoic ring (FA$_7$) are very widespread in bacteria, but are never accompanied by cyclopropane acids (Christie, 1970; Smith, 1970). Phytomonic acid, identical to lactobacillic acid, was first discovered in the lipids of Agrobacterium tumefaciens (Chargaff and Levine, 1938; Velick and Anderson, 1944). Its structure corresponds to that of D- or L-cis-11-12-methylenoctadecanoic acid (Hofmann et al., 1958; Graven and Jeffery, 1960):

\[
\text{H}_2\text{C}-(\text{CH}_2)_{13} \text{CH}-(\text{CH}-(\text{CH}_2)_{9}) \text{COOH.}
\]
Lactobacillic acid has likewise been isolated from Lactobacillus arabinosus and L. casei (Hoffman and Sax, 1953), L. delbrückii (Hoffman et al., 1957; Cronan, 1968), Brucella abortus and B. melitensis (Thiele et al., 1969). At length, C_{13}, C_{15}, C_{17}, C_{19} and C_{21} fatty acids with propanoic ring were shown to be present in lipids of P. pestis (Asselineau, 1961; Alimova and Boikova, 1967), Bacillus subtilis (Asselineau, 1961), Escherichia coli (O'Leary, 1959; Dauchy and Asselineau, 1960; Knivett and Cullen, 1965; Weinbaum and Panos, 1966; Silbert et al., 1968; Alimova and Gurskii, 1972), pleuropneumonia-like organisms (O'Leary, 1962), Clostridium butyricum (Goldfine, 1961; Goldfine and Bloch, 1961; Hildebrand and Law, 1964), Salmonella typhi murium (Akashi, 1939; Gray, 1962; Vaczi et al., 1964/65, 1965/66; Alimova et al., 1969b), Shigella flexneri and Proteus vulgaris (Vaczi et al., 1964/65, 1965/66), Serratia marcesens (Bishop and Still, 1963), Agrobacterium tumefaciens (Lam et al., 1963; Hildebrand and Lam, 1964), Rhodomicrobium vanniellii (Park and Berger, 1967), Azotobacter agilis (Hildebrand and Lam, 1964), Haemophilus parainfluenzae (White and Cox, 1967), B. abortus and B. melitensis (Thiele et al., 1969), Vibrio cholerae (Brian and Gardner, 1968), Streptococcus uberis (Macleod and Miller, 1967), Mycobacterium tuberculosis human (Minnikin and Polgar, 1966, 1967), and the extremely thermophilic bacteria of the Yellowstone springs (Bauman and Simmonds, 1969). Dimycolate(?) of arabinose, one of the acids of which (monobasic) contains two cyclopropanoic groups, has been isolated from Mycobacterium marinum. This acid is identical to α-cansamycolic (?) acid (Maud and Georges, 1968).

* Spelling uncertain; I could not find these in any source (Trans.).
It should be noted that C17\(\alpha\) - and C19\(\alpha\) - acids are the most common acids in the lipids of bacteria, while the C17\(\alpha\) present in large quantities in *E. coli* is a cis-9,10-methylenehexadecanoic acid, i.e. a homologue of lactobacillic acid (Kaneshiro and Marr, 1961). A definite ratio of C19:0\(\alpha\) - and C17:0\(\alpha\) - acids is characteristic of individual species of bacteria. Thus, the acid C19:0\(\alpha\) predominates in the lipids of *Agrobacterium tumefaciens* (Kaneshiro and Marr, 1962), *L. casei* (Chalk and Codicek, 1961), and *Streptococcus lactis* (Macleod et al., 1962). A large amount of C17:0\(\alpha\) - acid as opposed to C19:0\(\alpha\) has been noted in *E. coli* (Kaneshiro and Marr, 1961), *S. marcescens* (Bishop and Still, 1963), *Salmonella typhi murium* (Gray, 1962), *Agrobacterium aerogenes* (O'Leary, 1962), and *Clostridium butyricum* (Goldfine and Bloch, 1961). A great quantity (41.9 - 48.9%) of FA\(_{unev}\), a considerable part of which consisted of acids with propanoic cycles (38.0%) has been discovered in 12 cultures of *S. typhi* (Alimova et al., 1969b).

The study of the fatty acid content in bacteria lipids has shown that gram-positive bacteria contain large amounts of fatty acids with normal chains of carbon atoms and of branched acids, and comparatively few unsaturated acids. In gram-negative bacteria FA\(_{br}\) are practically non-existent, while FA\(_{\alpha}\) are present in considerable quantities. An exception is the fatty acid composition of the genera *Lactobacillus* and *Clostridia*, which resembles that of the gram-negative bacteria (Kates, 1964).

Cyclopropanoic acids (sterculic: 9,10-methyleneoctadec-9-enic, and malic: 8,9-methyleneheptadec-8-enic), which are accompanied in small quantities by FA\(_{\alpha}\) (dihydrosterculic and dihydromalic) are peculiar to
plants of the mallow and sterculia families (Smith, 1970; Christie, 1970; and others). In addition, cyclopropanoic acids are concentrated in the triglycerides of plant tissues (Jano et al., 1972a).

**De novo BIOSYNTHESIS OF BRANCHED HIGHER FATTY ACIDS AND OF THOSE WITH AN UNEVEN NUMBER OF CARBON ATOMS IN A CHAIN OF NORMAL STRUCTURE**

A study of the fatty acid content of *Candida tropicalis* showed that FA$_{unev}$ structure depends on the content of alcohols with an uneven number of carbon atoms in the culture medium (Alimova et al., 1968). These acids are formed exclusively by oxidation by candida enzymes corresponding in length to the hydrocarbon chain of the H-alcohols of the medium. Analogous findings have been obtained in experiments on *Nocardia* (Davis, 1964) and *Micrococcus cerificans* (Makula and Finnerty, 1968). Our own research showed that FA$_{unev}$ are formed in the cells of *C. tropicalis* whenever the sole source of carbon in the culture medium is glucose or a hydrocarbon with an even number of carbon atoms, but to a considerably lesser degree (Alimova et al., 1968). Similar results have been obtained in experiments on *C. petrophillum* (Mizuno et al., 1966), *C. utilis* (Brown and Rose, 1969), *C. lipolectica* (Klug and Marcovetz, 1967), and likewise *Brevibacterium* sp. (JOB5), *Mycobacterium* sp. (OPS) and *Nocardia* sp. (OC2A) (Dunlap and Perry, 1967). It is interesting to note that in the lipids of vegetative cells of the thermophilic bacteria *Bacillus* sp. a greater quantity of FA$_{unev}$ containing 15 – 17 carbon atoms is found in cells using glucose as a carbon source than in cells using acetate (Daron, 1970). A study done with 10 strains of *C. tropicalis* and 10 strains of *C. robusta* raised under identical conditions in an agar medium revealed the formation of C$_{11}$, C$_{15}$ and C$_{17}$ acids, the total content of which varied from trace quantities to 4.5% in the first group.
and 2.9 - 8.5% in the second (Ciarlini et al., 1965).

There is no doubt that the formation of fatty acids in the cells of candidae raised in media containing H-alkanes* is connected with the oxidation of the terminal group of the latter, inasmuch as the newly formed acids, for the most part, correspond in chain length to the substratum. The established similarity in qualitative composition between fatty acids of candidae raised on glucose and hydrocarbons with an even number of carbon atoms can be explained by the fact that the synthesis of fatty acids by fungi which use these substrata as their sole source of carbon can proceed basically at the expense of such substrata, like acetyl-CoA, which forms as they degrade. The formation of FA\textsubscript{unev} in this growth medium testifies to the endogenous origin of a substratum for biosynthesis.

It can be posited that the human organism also contains enzymatic systems capable of the de novo synthesization of FA\textsubscript{unev}. Thus, the study of lipidic exchange in humans (Alimova et al., 1970) and animals (Kostromitina, 1968; Alimova et al., 1969) showed that these enzymatic systems are intensively activated in the presence of certain diseases, leading to an increase in the quantity of fatty acids in the blood and in other tissues.

Direct and indirect evidence of the ability of the enzymatic systems of a living organism to catalyze de novo a synthesis of FA\textsubscript{unev} makes it possible to raise the question of the nature and origin of the substrata essential for this process. In experiments on soluble enzymatic systems obtained from the liver, brain, intestinal mucous membrane and fatty tissue from the ovarial lobes of rats (Horning et al., 1961; Vagelos et al., 1962) it was shown that in the higher fatty acids, C\textsubscript{2} units are quickly absorbed by

* or n-alkanes? (Sorry, I could not find this one. - Trans.)
malonyl-CoA. For synthesis of $\text{FA}_{\text{unev}}$, the presence of propionyl-CoA was required; for isoacids with an even number of carbon atoms, isobutyryl-KoA or isocaproyl-KoA; for isoacids with an uneven number of carbon atoms, isovaleryl-KoA; and for anteisoacids with an uneven number of carbon atoms, $\alpha$-methylbutyryl-KoA.

When propionyl-KoA is present as the substratum, the enzymatic system of the pigeon catalyzes the biosynthesis of heptadecanoic acid in the quantity of 70%, while in the presence of butyryl-KoA it catalyzes stearic acid in the quantity of 85% (Bressler and Wakil, 1961). Administration of propionic acid to mice with their food (Tove, 1959) or of $\text{C}^{14}$-propionate intravenously (Favarger and Gerlach, 1966) led to the biosynthesis of long-chained saturated and monoethenoic (?) $\text{FA}_{\text{unev}}$ in considerable quantities. In vivo experiments on rats (Zabin and Bloch, 1950, 1951) have demonstrated the incorporation of the isopropyl group of isovaleric acid into the fatty acids to the same degree as acetate. Injection of $1-\text{C}^{14}$-valerate into the jugular veins of cows led to the incorporation of the tagging into higher fatty acids with even and uneven numbers of carbon atoms in the butterfat (Gerson et al., 1960). The introduction of valine as 5% of the diet of rats raised the content in skin lipids of $\text{FA}_{\text{br}}$ with an even number of carbon atoms; leucine as 5% of the diet raised the content of $\text{FA}_{\text{br}}$ isostructures with an uneven number of carbon atoms; isoleucine as 5% raised the content of $\text{FA}_{\text{br}}$ anteisostructures with an even number of carbon atoms and $\text{FA}_{\text{unev}}$ (Grigor et al., 1970).

The abovementioned substrata serve as precursors for the biosynthesis of corresponding higher fatty acids in the bacteria $\text{B. subtilis}$, $\text{B. megaterium}$,

* Monoethenoic would seem correct here. The Russian original has monoenoic (perhaps a variation?) which I could not find in any source. - (Trans.)
Shizosaccharomyces liquefaciens, Sarcina lutea, Micrococcus lysodeicticus, Ruminococcus flavefaciens, Bacterioides succinogenes and others (Wagner and Foster, 1960; Allison and Bryant, 1961; Lennarz, 1961; Kaneda, 1963, 1966, 1971; Albro and Dittmer, 1969; Scandella and Kornberg, 1969; Baraud et al., 1970). The isovaleric group of branched higher fatty acids with an even number of carbon atoms is formed by microorganisms mainly from the isovaleric group of valine, while another such group of fatty acids, with an uneven number of carbon atoms in their chain is formed from the isovaleric group of leucine. It has been proposed (Kaneda, 1968) that the incorporation of valine into fatty acids in microorganisms may take place due to the involvement in the biosynthetic process of the enzymatic system, which catalyzes the condensation of α-ketoisovalerate and acetyl-CoA as well as the formation of α-ketoisocapronate (Jungwirth et al., 1961; Calvo et al., 1962; Gross et al., 1962; Strassman and Ceci, 1962). The process is accompanied by decarboxylation. Similar enzymatic systems have been discovered in a variety of microorganisms.

A chart advanced by Kaneda (1963b) represents the biosynthesis by bacteria of iso-fatty acids with even and uneven numbers of carbon atoms from valine and leucine:

\[
\begin{align*}
\text{H}_2\text{C} & \text{CH} \text{CHOH} \\
\text{H}_2\text{C} & \text{CH} \text{COOH} \\
\text{H}_2\text{C} & \text{CH} \text{CH} \text{COOH} \\
\text{H}_2\text{C} & \text{CH} \text{CH} \text{SOA} \\
\text{H}_2\text{C} & \text{CH} \text{C} \text{SOA} \\
\text{H}_2\text{C} & \text{CH} \text{CH} \text{C} \text{SOA} \\
\text{H}_2\text{C} & \text{CH} \text{CH} \text{CH} \text{COOH} \\
\text{H}_2\text{C} & \text{CH} \text{CH} \text{CH} \text{SOA} \\
\text{H}_2\text{C} & \text{CH} \text{CH} \text{CH} \text{SOA} \\
\text{H}_2\text{C} & \text{CH} \text{CH} \text{CH} \text{SOA} \\
\end{align*}
\]
Experiments on *M. lysodeicticus* have demonstrated the possibility of synthesis of anteiso-acids through the condensation of malonyl-CoA and α-methylbutyryl-CoA, the product of the degradation of isoleucine (Lennarz, 1961). Also, on the basis of the results of research on *B. subtilis*, a mechanism for the biosynthesis of optically active anteiso-fatty acids in bacteria, depicted in a chart proposed by Kaneda (1966b) has been postulated:

\[ \text{Alloisoleucine} \xrightarrow{\text{g}} \text{d(+)-α-keto-β-methylvalerate} \xrightarrow{\text{Precursors}} \text{L-Isoleucine} \xrightarrow{\text{b}} \text{D(--)-α-methylbutyryl-CoA} \xrightarrow{\text{D(-)12-methyltetradecanoic acid}} \text{D(+)-14-methylhexadecanoic acid} \]

Processes d and g possibly catalyze alanyldehydrogenase - an enzyme which has a broad substratum specificity.

It has been shown that the terminal part of the acids is synthesized from pyruvate and α-ketobutyrate (which originates, probably, from threonine) through the L-keto-β-methylvalerate mechanism for de novo synthesis of L-isoleucine. L (+) α-keto-β-methylvalerate (α-ketoacid, which corresponds to L-isoleucine) can fit into the terminal C₅-part of the molecules of synthesized acids without altering the stereoconfiguration of a carbon atom in β-position. Obviously, this is achieved by the formation of D (--) α-methylbutyryl-CoA. D (--) α-keto-β-methylvalerate (α-ketoacid, which corresponds to L-alloisoleucine) fits in after transformation into the corresponding L-isomer. For the synthesis D (+) α-methylbutyrate, the stereostructure of which is close to that of L-isoleucine, but not its L-isomer, is used. In all experiments a D-isomer of the anteisofatty acids
was a product, regardless of the stereoconfiguration of the precursors. Clearly, the synthesis of optically active fatty acids by microorganisms is not only a result of the presence of one particular precursor, but also a result of the capacity for stereospecific choice of the precursor at a certain stage (or stages) of synthesis.

The quantity of synthesized fatty acids depends on the content of the biotype in the culture medium and the timespan of the culture. Any reduction in the concentration of the biotope leads to a reduction in the overall quantity of fatty acids, but the proportion of the sum of 12-methyltetradecanoic and 14-methylhexadecanoic acids to the other acids increases considerably.

The data examined permit one to postulate that in macro- and microorganisms the comparative intensification of the process of biosynthesis of FA vener fatty acids of iso- and anteiso-structure is a function of the accessibility of corresponding precursors of the terminal groups of fatty acids. Such precursors are formed by the degradation of valine (propionyl-CoA, isobutyryl-CoA), isoleucine (propionyl-CoA, α-methyl-butyryl-CoA and leucine (isovaleryl-CoA). It has been shown that propionyl-CoA is likewise formed by the degradation of aliphatic amines (Atchley, 1948; Coon et al., 1955; Kinnory et al., 1955). It is also formed during the decarboxylation of CoA-produced succinate (a reversible process), as shown with bacteria (Carson and Ruben, 1940; Delwiche, 1948; Johns, 1948, 1949; Barban and Ajl, 1951; Delwiche et al., 1953, 1954; and Wheatley, 1963), tissue from rats (Lardy and Peansky, 1953; Lardy and Adler, 1956; and Erfle et al., 1964), bulls and guinea pigs (Elavin et al., 1956; Friedberg et al., 1956; Lardy and Adler, 1956; Beck et al., 1957), sheep (Mazumder and Sasakawa, 1961), chicks (Erfle et al., 1964), pigs (Flavin and Ochoa, 1957) and other organisms.
In *Bacterioides ruminicola* the formation of propionate through a direct restoration from the products of the oxidation of glucose, bypassing the dicarboxylic acids (Wallnöfer and Baldwin, 1967) has been demonstrated. There are reports of propionate having been formed during the degradation of dimethyl-β-propiothetin (dimethyl-2-carboxyethyl-sulphone chloride) (Motohiro, 1962), found in seaweed in quite large quantities (Challenger, 1959; Ackman, 1965). The C₃-unit can form from the oxidation and break-up of saturated fatty acids of γ-oxyacyl-CoA-derivatives by way of γ-δ oxidation (Dimick et al., 1969).

The successes achieved in the study of the mechanism of the biosynthesis of the higher fatty acids testify that the de novo biosynthesis of branched, iso- and anteisostructure FAunev takes place in vivo in the very same way as that of fatty acids with an even number of carbon atoms (Popjak, 1952; Hele, 1958; Green and Wakil, 1960; Wakil, 1961, 1962, 1970; Gulyi, 1961; Shabanova, 1961; Vagelos, 1964; Budnitskaya, 1965; Grozdova, 1966; Lynen, 1967; Phillips et al., 1970).

Thus, the de novo biosynthesis of higher fatty acids of the indicated structure in mammals, birds, plants, yeasts and bacteria amounts to the condensation of propionyl-CoA or valeryl-CoA or short-chained branched acyls of CoA (isovaleryl-CoA, α-methylbutyryl-CoA and others) and malonyl-CoA. As a result, the terminal part of the carbon chain in the synthesized molecule mirrors the structure of the carbon skeleton of the substratum, and the other carbon atoms, including those of the carboxyl group, are borrowed from malonyl-CoA.

As for enzymatic systems catalyzing a synthesis of higher fatty acids — obviously, in a majority of the higher organisms and the yeasts it is connected
with an indivisible multienzyme complex called "synthetase of higher fatty acids", while in bacteria it breaks down into several components. As is well known, the multienzyme complex has been isolated from yeasts (Lynen et al., 1960; Lynen, 1961, 1962, 1967), bacteria (Vagelos, 1959, 1964; Vagelos and Alberts, 1960; Vagelos et al., 1963; Alberts, 1963), hyaloplasm from rat livers (Bressler and Wakil, 1961, 1962), fat tissue from rats (Martin et al., 1961) and other animal tissues. The possible biosynthesis of FA unequal, as well as acids with an even number of carbon atoms by micro- and macroorganisms in the process of the oxidation of hydrocarbons should likewise be taken into consideration. The surveys of L.A. Mavrinaya (1966), E.P. Pozanovaya (1967) and I.N. Pozmogovaya (1968) have thrown light on the mechanism for this in microorganisms.

In the organisms of animals and bacteria, fatty acids with uneven and even numbers of carbon atoms in which the methyl groups are not located around the terminal carbon atoms of the molecule have been discovered. Among them have been discerned fatty acids with one or several lateral methyl groups. The formation of a lateral chain is seen as taking place via the mechanism of the condensation of propionate (through its α -carbon atom with the end groups of the initial acid) (Polgar, 1951; Gerzon et al., 1956; Woodward, 1956). Propionate is incorporated in the biosynthesis of tuberculostearic (C₁₉) acid and mycocerosic (C₃₂) acid in Mycobacterium tuberculosi H37Ra (Lederer, 1961; Gastambide-Odier et al., 1963), in the biosynthesis of phthioic acid (C₂₇), synthesized by M. tuberculosis (Dupré bovine strain) Gastambide-Odier et al., 1966), and also in the biosynthesis of a branched C₁₆-acid by brevibacterium sp. (JOB5), Nocardia sp. (OC2A) and Mycobacterium sp. (OFS) (Dunlap and Perry, 1967).
It is possible that higher fatty acids with a multibranched carbon chain may be synthesized by way of a multiple condensation of α-substituted malonyl-CoA derivatives (methylmalonyl-CoA or ethylmalonyl-CoA) with one molecule of the initial fatty acid:

The formation of methylmalonyl-CoA has been observed in thin sections of rat liver and in extracts from pig hearts, heart muscle from rats and rat and sheep kidneys, in the presence of propionyl-CoA, ATPH, Mg²⁺ and Cl₄O₂ (Flavin, 1955; Flavin et al., 1955; Katz and Chaikoff, 1955). The reaction that forms methylmalonyl-CoA is catalyzed by propionyl-CoA carboxylase, which is just as widespread in nature as is acetyl-CoA carboxylase (Flavin et al., 1956, 1957; Kaziro et al., 1961; Lane et al., 1962).

Acids with one methyl lateral group with an uneven number of carbon atoms can also be synthesized through the addition to the fatty acid of a radical with one carbon atom (C₁) from the methyl group of methionine or formyl. This has been shown in Mycobacterium phlei in the case of the biosynthesis of methylstearic acid from stearic acid (Lennarz et al., 1962) and methylpalmitic acid from palmitic acid (Scheuerbrandt and Bloch, 1962):
Later it was shown that a proton is lost in the course of the transfer of the methyl group of the methionine (Jaureguiberri et al., 1964, 1965). The reaction is accompanied by a shift of the olefin proton from the 10th atom to the ninth atom of the hydrocarbon chain of the unsaturated fatty acid (Bristol and Schroepfer, 1966; Lenfant et al., 1966):

\[
\begin{align*}
R_1 & \quad R_2 \\
\text{C}_\text{H}_\text{C} & \quad \text{C}_\text{H}_\text{C} \\
\text{Cl}_\text{2} & \quad \text{Cl}_\text{2}
\end{align*}
\]

Proof of the basic assumptions in the proposed mechanism was furnished by the isolation of tagged 10-methylenestearic acid from cellular homogenates of \textit{M. phlei} incubated with \textsuperscript{14}C-methylmethionine (Jaureguiberri et al., 1966). The nature of the endogenous lipidic acceptor, the donor of the methyl group and the hydrogen participating in the reduction of the 10-methylene group can be expressed in terms of the following reactions (olefin fatty acid acyl) phospholipid + S-adenosylmethionyl → (methyleneacyl) phospholipid + S-adenosylhomocysteine; and (methyleneacyl) phospholipid + NADPH + H\textsuperscript+ → (methylacyl) phospholipid + NADPH\textsuperscript+.

Most recently it has been shown (Akamatsu and Law, 1970) that the enzyme of \textit{M. phlei} that catalyzes the reaction between the S-adenosylmethionine and olefin chains in phospholipid molecules is located in those membranes.
where its lipidic substratum is localized. S-adenosyl-L-methionine is a more efficient donor of C1-units needed for the synthesis of 10-methylenestearate than methionine, serine or formate. A\textsuperscript{3}-olefin C\textsubscript{16} and C\textsubscript{18} fatty acids of phosphatidylglycerols, phosphatidylinositol and phosphatidylethanolamines can serve as substrates for the reaction. The enzyme catalyzes the alkylation of the fatty acids located in positions one or two of the glyceride molecule. Free oleic acid exhibits no stimulant action on this process. The enzyme is not stimulated by detergents. Biosynthesis of tuberculostearic acid increases during the stationary phase of growth (Lennarz et al., 1963b).

**BIOSYNTHESIS OF FATTY ACIDS WITH A PROPANOIC RING**

The process of the biosynthesis of FA\textsubscript{\textgamma} leads to the inclusion of a methylene bridge, originating from the methylene group of methionine, at the place of the dual link of monoolefinic acid. The biosynthesis of C\textsubscript{17\textgamma} and C\textsubscript{19\textgamma}-acids in the systems of the growing cells of *E. coli*, *Lactobacillus arabinosis*, *Serratia marcescens*, *Clostridium butirricum*, *Agrobacterium tumefaciens*, *A. aerogenes* and *Lactobacillus casei* have received the most detailed study.

S-adenosylmethionine (O'Leary, 1962; Zalkin et al., 1963; Hildebrand and Law, 1964; Thomas and Law, 1966; Cronan, 1968) is an active donor of methyl groups, even though little activity has been noted in the other monocarboxic donors: sodium propionate, L-serine, sodium formate, formaldehyde, methanol and glycine (O'Leary, 1959; Liu and Hofmann, 1962; Law et al., 1963). Only two hydrogen atoms from the methyl group of methionine are incorporated into the methylene bridge of the FA\textsubscript{\textgamma} as the latter takes shape. The protons of the vinyl group of monoolefin undergo no change during the
conversion (Pohl et al., 1963; Polachek et al., 1966):

\[
\begin{align*}
\text{Adenosyl} & \quad \overset{S-(\text{CH}_2)_2\text{CH}(\text{NH}_3)^+\text{COO}^-}{\longrightarrow} \quad \overset{\text{H}^+}{\text{Adenosyl}} \\
& \quad \overset{\text{S-}-(\text{CH}_2)_2\text{CH}(\text{NH}_3)^+\text{COO}^-}{\longrightarrow} \\
& \quad \overset{+\text{R-C}=C-R_1 \to \text{R}-\text{C}=-\text{R}_1}{\longrightarrow} \quad \text{Adenosyl} \\
& \quad \overset{\text{S-}-(\text{CH}_2)_2\text{CH}(\text{NH}_3)^+\text{COO}^-}{\longrightarrow}
\end{align*}
\]

It can be postulated that this mechanism is also inherent in plant organisms (Smith and Bu'Lock*, 1964, 1965; Johnson et al., 1967; Law, 1971; Jano et al., 1972a). In experiments with C\textsuperscript{14}-H\textsubscript{3}-methionine and 2-C\textsuperscript{14}-acetate (Jano et al., 1972b; and others) the following reaction sequence in the biosynthesis of cyclopropanoic acid and cyclopropenoic acid was shown:

oleic acid (+ CH\textsubscript{2} from methionine) \(\rightarrow\) dihydrosterculic acid (--H\textsubscript{2}) \(\rightarrow\) sterculic acid (\(\alpha\)-oxidation \(\rightarrow\) malic acid (+H\textsubscript{2}) \(\rightarrow\) dihydromalic acid; the latter, moreover, is a product of the \(\alpha\)-oxidation of dihydrosterculic acid.

The substratum for the biosynthesis of FA\textsubscript{V} in bacteria, \textit{in vitro} as well as \textit{in vivo} is provided by monoolefin fatty acids of intact phospholipids, principally phosphatidylethanolamines (Zalkin et al., 1963; Chung and Law, 1964; Hildebrand and Law, 1964; Thomas and Law, 1966; Kanemasa et al., 1967; Cronan, 1968). Unsaturated fatty acids and FA\textsubscript{V} form ester bonds in a \(\beta\)-arrangement of phosphatidylethanolamine molecules; saturated fatty acids, in a \(\gamma\)-arrangement. The position of FA\textsubscript{V} in phosphatidylethanolamines incubated with a preparation of cyclopropanesynthetase in the presence of S-adenosylmethionine correspond to those of unsaturated acids in substrata (Hildebrand and Law, 1964). The least intensive biosynthesis recorded for phosphatidylethanolamine was in comparison with phosphatidylglycerine and

* ? (spelled thus in both the text and the bibliography of the original) Perhaps Bullock? -- Trans.
cardiolipid (Kanemasa et al., 1967; Cronan, 1968). It has been noted that in addition to 9,10-methylenehexadecanoic acid and cis-11,12-methyleneoctadecanoic (lactobacillic) acid, typical of E. coli (Chalk and Kodicek, 1961; Kates, 1964), Thiobacillus Thiooxidans bacteria synthesize 11,12-methylene-2-oxyoctadecanoic acid (Knoche and Shively, 1969). Catalysis of the biosynthesis of FA_v has been proven in vitro for cell-free preparations of Serratia marcescens and Clostridium butyricum (Zalkin et al., 1963), Aerobacter aerogenes and Lactobacillus arabinosus (O'Leary, 1965), E. coli (Cronan, 1968) and in a preparation of Clostridium butyricum purified roughly ten times over by the method of Chung and Law (1964).

Catalysis of a methylation reaction has been determined, but not absolutely specified, for phosphatidylethanolamine acids (Hildebrand and Law, 1964). The action of the alkylating cyclopropanesynthetase of the enzyme is stimulated by an anionic detergent. The part played by folic acid in the synthesis of 11,12-methyleneoctadecanoic acid in a culture of Lactobacillus plantarum and L. casei has likewise been demonstrated (Henderson et al., 1965).

In experiments on many species of bacteria it has been shown that the rate of formation of FA_v is almost linear and that it will persist to a great extent after a growth in the quantity of cells comes to an end. Increases in FA_v content in the latter phases of growth have been proven for E. coli (Marr and Ingraham, 1962; Knivett and Cullen, 1965, 1967; Cronan, 1968), Lactobacillus arabinosus (Croom and McNeil, 1961), Serratia marcescens (Kates et al., 1964; Alberts, 1963) and others. In E. coli, synthesis of C_{17v} increases sharply in the postexponential phase, as compared with the exponential phase (by 12 times), and there is a marked accumulation
of of C_{19\nu}-acid. Experiments with *E. coli* O-111 have shown that the accumulation of FA_{\nu} during the exponential, postexponential and stationary phases of growth runs parallel to a decline in C_{16:1} and C_{18:1} fatty acid content and that, moreover, these changes correlate with changes in methionine content (Alimova *et al.*, 1972). The dependence of the quantity of FA_{\nu} on the unsaturated acids content has been noted by other authors as well (Karkas *et al.*, 1972). Thus, the intensity of the biosynthesis and accumulation of FA_{\nu} depends on the phase of growth of the population.

Many data, without a doubt, testify to a certain role of FA_{\nu} in the biology of microorganisms. Thus it is known that the acid C_{19\nu} can serve as a growth factor in *E. coli* along with the acids cis-C_{18:0}, trans-C_{18:1} and C_{18:3}. This acid, included in large quantities in the fatty acid composition of membrane lipids, has a direct influence on its penetrability and, possibly, on the provision of energy for the transfer of matter (Schairer and Overath, 1969).

The increase in the synthesis of FA_{\nu} at the latter stages of growth is, obviously, a reaction of the organism to a decline in the intensity of the transfer of matter in bacteria caused by changing conditions of existence. This is all the more plausible because there are data (Hofmann and Sax, 1953; Dauchy and Asselineau, 1960; Gray, 1962) testifying to the ability of FA_{\nu} to strengthen the reproduction of bacteria and activate metabolism. It is possible that the cyclopropanoic ring protects the double bonds from oxidation (Law *et al.*, 1963). At the same time, the transformation of the double bond into a propanoic ring does not alter several important physical properties of the phospholipids (for example, the ability to form soluble lipidic micelles). Obviously, this kind of transformation does not change the
normal functioning of unsaturated fatty acids. The fact that \( FA_\nu \) are absent from many microorganisms fits in with this proposition. Defence of phospholipids from degradation during the stationary phase of growth should be considered a second possible function of \( FA_\nu \), in view of the fact that secondary synthesis of phospholipids during that time is hampered, yet the phospholipase activity of the cells is considerable (the phospholipidic synthetic index for idle cells amounts to only 0.15% of the index for growing cells) (Cronan, 1968). Sometimes the \( FA_\nu \), once formed, remain stable during the logarithmic and stationary phases of growth, but the phospholipid content does not decrease during the stationary phase.

In *Salmonella typhi* a tendency toward a rise in \( C_{19:0\nu} \) content has been noted in the lipids of cells as accompanying the acquisition of a resistence of levomycetin; the most detailed changes that have been recorded are those in the cell walls (Alimova *et al.*, 1969b). The correlation of resistence to the lipidic content of membranes and coatings in the gram-negative bacteria has likewise been revealed by other authors (Dunnick and O'Leary, 1970).

As for animals, here practically nothing is known about \( FA_\nu \). The presence of 11-cyclohexylundecanoic acid in trace amounts in the surplus fat of sheep and in butterfat from cows is apparently conditional to the activity of the microflorae of the rumen (Hansen, 1967). One recent study has shown the possibility of the biosynthesis of cyclopropyl long-chained fatty acids from cyclopropanecarbonic acid (tagged with carbon of the carboxylic group) by mammalian tissues *in vitro* (Duncombe and Rising, 1968). When adipose tissue from the lobes of the testicles of rats and guinea pigs, and also thin sections of liver or supernated fluid obtained by
fast centrifugation of homogenates of rat liver were incubated with C\textsuperscript{14}-
cyclopropanecarbonic acid, radioactivity was discovered in the composition
of five long-chained fatty acids containing cyclopropanoic rings in the
adipose tissue:

\[
\text{H}_3\text{C} - \text{CH} - (\text{CH}_2)_n - \text{COOH.}
\]

A diversity of variations of experiments with tagged and untagged
precursors (acetate, propionate, isobutyrate) in the presence of glucose,
stimulants (HCO\textsubscript{3} -, malonate and others) and inhibitors (avidin) on fatty
acid synthesis have shown that the cyclopropanoic ring is situated in the
\(\omega\)-position, but the remaining part of the fatty acid is synthesized along
malonate lines. Duncombe and Rising (1968) proved that the cyclopropanoic
ring does not degrade when incorporated into the fatty acids of animal
tissues.

When mitochondria or homogenates of whole rat liver are incubated with
tagged \textit{cis}-9,10-methyleneoctadecanoic acid or \textit{cis}-9,10-methylenehexadecanoic
acid (biosynthesized by \textit{Clostridium butyricum}), the methylene carbon of the
cyclopropanoic rings does not oxidize to CO\textsubscript{2} while the hydrocarbon chains
are contracting. As a result, \textit{cis}-3,4-methylenedodecanoic acid and \textit{cis}-
methylenedodecanoic acid accumulate in the incubating mixture (Chung, 1966).\n\textit{Cis}- or \textit{trans}-3,4-methylenedodecanoic acids accumulate in the adipose tissue
of rats that have had synthetic \textit{cis}- or \textit{trans}-9,10-methyleneoctadecanoates
introduced into their diet (Wood and Reiser, 1965). At length it was
demonstrated that \textit{cis}-9,10-methyleneoctadecanoic and \textit{cis}-methylenehexadecanoic
acids act as substrates for the acyltransferases of the microsomes of rat
livers that play a part in the biosynthesis of phospholipids (Okuyama \textit{et al.},
In the organism of the rat, 2-amino-3-methylenecyclopropylpropionate (a hypoglycine-hypoglycemic agent) is quickly transformed through the metabolic process (in vivo) into methylenecyclopropylacetate, which then accumulates (Holt, 1966). Cyclopropane itself and its methyl, ethyl and vinyl esters are biochemically inert and are excreted unchanged by animal organisms (Williams, 1959).

It is known that cyclopropanecarbonic acid can contribute to depressing the oxidation of fatty acids (Williamson and Wilson, 1965; Senior and Sherratt, 1967). Experiments conducted in vivo with rats and in vitro with rat and chicken livers have demonstrated the inhibition of acyldesaturase of fatty acids by cycloproponoic fatty acids. The introduction of 1-C14-methylstearate, dissolved in the oil of Sterculia foetida (a source of cyclopropanoic fatty acids) into the organism of rats perorally and into the homogenates of livers in vitro directly, decreased to a considerable degree the process of the desaturation of stearic acid in adipose tissue and especially in the liver. By increasing the dose of this oil it was possible to halt the process altogether. The inhibiting effect of sterculic acid and the somewhat weaker effect of malic acid on the desaturase of chicken livers has likewise been shown (Jahnson et al., 1969).

It is believed that the mechanism for the inhibition of acyldesaturase consists in a non-reversible bonding of the sulphhydryl groups of the enzyme's catalytic center by the cycloproponoic groups contained in the fatty acids of Sterculia foetida (Raju and Reiser, 1967, 1972). In addition, a bond is formed between the C9- or C10-atoms, for example, by the sterculyl-CoA and SH-groups of the enzyme (Jahnson et al., 1969).
Cyclopropanocarbonic acid induces a hypoglycemic effect in guinea pigs and monkeys. Its action on rats and humans in this regard is less effective, but in all animal species tested it displays the properties of a synergist of insulin (Stewart, 1962). Its action is believed to be linked with the formation of cyclopropyl fatty acids (Duncombe and Rising, 1968).

**OXIDATION OF HIGHER FATTY ACIDS OF ISO- AND ANTEISOSTRUCTURE AND OF THOSE OF NORMAL STRUCTURE WITH AN UNEVEN NUMBER OF CARBON ATOMS**

Study of the mechanism of β-oxidation of fatty acids in the enzymatic systems of tissues of animal, plant and bacterial cells has shown, in accordance with the classic experiments of Knoop and Dakin (1904 and 1911 resp.) that FA_{unev} and likewise acids of iso- and anteisostructure act as substrates of β-oxidation enzymes. The conversion of propionyl-CoA, the end product of the β-oxidation of FA_{unev}, is achieved basically through a preliminary carboxylation, catalyzed by propionyl-CoA-carboxylase, into methylmalonyl-CoA, isomerized into succinyl-CoA (Kaziro et al., 1961, 1965). This reaction is reversible and is catalyzed, so the theory goes, by two enzymes: methylmalonylrasemass catalyzes the conversion of the D-stereoisomer of methylmalonyl-CoA into the L-isomer; methylmalonylmutase, the conversion of the L-isomer into succinyl-CoA (Mazumder and Sasakawa, 1961; Mazumder et al., 1963; Rettley and Lynen, 1964; Sprecher et al., 1964; Cannata et al., 1965). The further transformation of succinyl-CoA is due to the sequence of the citric acid cycle within the Krebs cycle. β-oxidation of isostructured fatty acids with even and uneven numbers of carbon atoms results mainly in the formation of isobutyryl- and
isovaleryl-CoA, respectively. From acids of an anteisostructure with an uneven number of carbon atoms, a mixture of acetyl- and propionyl-CoA is formed.

In addition to β-oxidation of higher fatty acids, the sequence for α-oxidation has been discovered in plant tissues. α-oxidation is defined as a repetition of the cycles of the successive catalysis of a reaction leading to the oxidation of free fatty acids from C₁₈ to C₁₃, with the simultaneous decarboxylation and contraction of the hydrocarbon chain of the fatty acid in each cycle by one carbon atom (Stumpf, 1970):

\[
\begin{align*}
\text{Peroxidase of fatty acids} & \quad \xrightarrow{\text{H}_{2}O_{2}} \xrightarrow{\text{oxidoreductase}} \xrightarrow{\text{Aldehyde dehydrogenase}} \xrightarrow{\text{NAD}^{+}} \xrightarrow{\text{NADH}} \xrightarrow{\text{NAD}^{+}} \xrightarrow{\text{NADH}} \xrightarrow{\text{NADPH}} \xrightarrow{\text{NADPH}} \\
\text{R-CH}_2\text{-COOH} + 2\text{H}_2\text{O}_2 & \quad \rightarrow \text{CO}_2 + \text{R-C-H} + 3\text{H}_2\text{O} \\
\end{align*}
\]

The α-oxidation process has been discovered in mitochondriae, microsomes and cell-free extracts from the seedlobes of germinants of the peanut and the safflower and from the leaves of the peanut, the castor-bean and the pea, and in extracts from the acetone powder of germinant peas. The oxidation systems of the seed-lobes and leaves of plants differ. In the former, under the effect of peroxidase, hydrogen peroxide in the generative system oxidizes the α-carbon atom of the fatty acid to aldehyde, while at the same time decarboxylation occurs. FA_{unev} provide the best substratum. The oxidizing system of leaves requires molecular oxygen (Hitchcock and James, 1966), but not hydrogen peroxide. L-α-oxyacids, which are utilized before the fatty acids contracted by one carbon atom, represent the first product of the reaction:

\[
\begin{align*}
\text{R-CH}_2\text{-COOH} & \quad \xrightarrow{\text{NAD}^{+}} \xrightarrow{\text{HAD}^{+}} \xrightarrow{\text{HADH}} \xrightarrow{\text{NADPH}} \xrightarrow{\text{NADPH}} \\
\text{L-R-COH-COOH} & \quad \rightarrow \text{R-COOH} + \text{O}_2 + \text{H}_2 \text{O} \\
\end{align*}
\]
The system is stereospecific: \(\text{D-}\alpha\text{-oxyacid}\) is not metabolized. When the fatty acids are oxidized with acetone powder from pea leaves both isomers are formed, but the L-isomer undergoes further metabolism, while the D-isomer accumulates (Hitchcock et al., 1968).

The peroxidizing reaction requires no cofactors and is inhibited by cyanide, azide and imidazole. Aldehyde oxidation is further stimulated by aldehydedehydrogenase, the coenzyme of which is \(\text{NAD}^{+}\) (Martin and Stumpf, 1959).

The oxidation rates of 1-C\(^{14}\) palmitic acid under \(\alpha\)- and \(\beta\)-oxidation are roughly identical. Absence of a process of activation of the fatty acid to acyl-CoA should be considered an advantage of \(\alpha\)-oxidation, while the \(\alpha\)-oxidation process is more efficient in terms of energy.

Observations carried out in recent years lead us to believe that \(\alpha\)-oxidation occurs in mammalian tissues, notably in the brain and liver of rats (Mead and Levis, 1962, 1963; Hajra and Radin, 1963). \(\text{FA}_{\text{unev}}\) are the result. Intermediate products of this path of oxidation are \(\alpha\)-oxy- and \(\alpha\)-keto acid, which undergo decarboxylation (Davies et al., 1966). This reaction requires the presence of oxygen, \(\text{NADPH}\) and \(\text{Fe}^{3+}\), and optimum pH in 6.1 phosphate buffer and a 6.9 tris-buffer. The reaction is activated by the systems that lead to the formation of \(\text{H}_{2}\text{O}_{2}\), and is suppressed by catalase; azide has no influence on it. It has been proposed that SH groups are present in the composition of the active center of an enzyme (Lippel and Mead, 1968). Possibly the enzymatic system which stimulates \(\alpha\)-oxidation in an animal organism exercises its greatest influence in the metabolism of long-chained fatty acids (C\(_{20}\) and over), since such acids do not form
complexes with proteins (for example with albumin) and therefore metabolize very slowly (Gatt and Shapiro, 1960; Fulco and Mead, 1961; Fulco, 1967). α- and β-oxidation of stearic acid has been discovered in the cells of the simplest *Tetrahymena pyriformis* and *Crithidia fasciculata* (Avine, 1968).

In recent years, experimentation on animals in vivo and observations of humans have shown that in mammalian tissues the multi-branched long- and medium-chained fatty acids are degraded through α-oxidation. This process takes on particular significance in the case of acids which have a lateral methyl group in β-position and which do not undergo β-oxidation. α-oxidation leads to the formation of α-methyl-derivatives, with the result that the β-carbon atom becomes accessible to the enzymatic systems. For example, the intermediate products of the oxidation of phytic acid are α-oxyphytanic, pristanic and pristenic acids. The last of these is the first α-β-unsaturated intermediate product of the classic β-oxidation of pristanic acid (Tsai et al., 1967, 1968, 1969):
It can be posited that the pristanic acid in mammal organisms, normally a product of the \( \alpha \)-oxidation of phytic acid, can be further degraded by \( \beta \)-oxidation, since all of the methyl groups of pristanic acid are in an \( \alpha \)-position with relation to the carboxyl group (Mize et al., 1966; Steinberg et al., 1967). This sort of reaction sequence has been noted in the course of the conversion of tagged \( ^{14} \text{C}-3,6\text{-dimethyloctanoic acid} \) in the organism of healthy humans (Eldjarn et al., 1966; Stokke et al., 1967), in experiments on the mitochondria of guinea pig livers (Stokke, 1968) and with guinea pig liver thin sections (Stokke, 1969a).

In mammals, loss of the capacity for \( \alpha \)-oxidation leads to an accumulation of \( \beta \)-branched acids. This, when the capacity for \( \alpha \)-oxidation is lowered in humans by Refsum's (?) disease, phytic acid accumulates significantly in the internal organs, all branches of the central nervous system, in the serum and in the urine (Klenk and Kahlke, 1963; Eldjarn et al., 1966; Kahlke and Wagener, 1966; Rake and Saunders, 1966; Karlsson et al., 1967; Steinberg et al., 1967; MacBrinn and O'Brien, 1968; Bonduelle et al., 1966; Kremer, 1966; Skribic and Cummings, 1969).

* Sorry; I could not locate this term in any source. Spelling uncertain — merely transliterated here. — Trans.
CONCLUSION

Fatty acids of the structures examined are widely distributed in living organisms and are synthesized de novo from substrata of endogenous and exogenous origin. The quantity of them in the tissues of a healthy organism is limited by the number of substrata, since they cannot be synthesized by mutual conversion of higher fatty acids with an even number of carbon atoms. These acids are mobilized from adipose tissue and undergo oxidation under the influence of specific enzymatic system, except for their propane or propene cycles, metabolizing just as do fatty acids of normal structure with an even number of carbon atoms (Nervi et al., 1966; Campbell and Hashim, 1969; Astbatsatur'yan and Alimova, 1969). The capacity for metabolism of fatty acids with an uneven number of carbon atoms is higher, clearly, in young animals (Kishimoto and Radin, 1959; Fulco and Mead, 1961).

To all appearances, the data being obtained today testify to the fact that the higher fatty acids with an uneven number of carbon atoms, branched acids, and those with a propane cycle in appropriate quantities are not only harmless to the organism, but also perform certain biological function, as has already been demonstrated for some of them. There are grounds for presuming that C$_{17}$-polyene acids are capable of exerting a positive effect, just as are the C$_{18}$-polyene acids, in cases of deficiencies of irreplaceable fatty acids (Schlenk and Sand, 1967).

LITERATURE


Ростовский государственный медицинский институт
Rostov State Medical Institute