

# Interconversions of the Saturated and Monounsaturated Fatty Acids

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**B**EFORE the advent of radioactive or isotopic tracers in the study of fatty acid metabolism, considerable evidence was available which indicated that the fatty acid composition of the body fats of mammals is determined in the following ways:

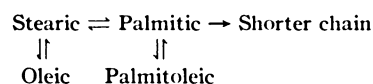
- (1) By direct deposition of dietary fat.
- (2) By synthesis from carbohydrate or other sources.
- (3) By alteration of fatty acids derived by the first two methods. It is with the third method that the present discussion is concerned.

The work of Schoenheimer and his collaborators, using deuterium, laid the groundwork for all the more recent studies of fatty acid interconversions. After feeding biosynthetically derived fatty acids containing deuterium, Schoenheimer and Rittenberg<sup>1</sup> found that the unsaturated fatty acids of the rats contained appreciable amounts of deuterium (one-fifth to one-half the amount of the saturated fatty acids isolated from the same rats). When biosynthetically prepared unsaturated fatty acids were fed, the saturated fatty acids contained one-fifth to one-fourth the deuterium found in the unsaturated fatty acids.<sup>2</sup> These amounts were the same as the deuterium content of the body water of the two rats. Since when water is the only source of deuterium, the saturated fatty acids of rats reach a maximum content about one-third that of the body water, Rittenberg and Schoenheimer concluded that at least two-thirds of the deuterium of the saturated

fatty acids was due to hydrogenation of the fed unsaturated acids. It is possible, however, that this conclusion is not justified, since in the experiments under consideration, the deuterium content of the saturated fatty acids could have been derived both from body water and from the break-down products of the unsaturated fatty acids.

In a further study, Stetten and Schoenheimer<sup>3</sup> found that deuteropalmitic acid was converted partially into stearic and palmitoleic acids. Bernhard and Schoenheimer,<sup>4</sup> on the other hand, found that linoleic acid obtained from rats maintained on a high-deuterium water contained little or no deuterium despite the fact that the other fatty acids showed appreciable amounts.

The results of three studies were summarized by Schoenheimer as follows:



The use of C<sup>14</sup> permitting the labeling of specific carbon atoms provided more definitive evidence on the interconversions of the saturated acids. Weinman and his co-workers<sup>5</sup> first administered palmitic acid (as tripalmitate), containing C<sup>14</sup> in the first or sixth carbons, to rats and monitored the rate of elimination of C<sup>14</sup>O<sub>2</sub>. Since no difference could be detected by this means in the rates of oxidation of the different types of palmitic acid, it was concluded that once oxidation of palmitic acid was initiated, it proceeded to completion with very little stabilization of shorter chain acids, such as myristic or lauric, taking place. When stearic acid labeled in the same manner was administered intravenously to rats as tristearin emulsion, somewhat different results were obtained.<sup>6</sup> In this case, the stearic acid labeled

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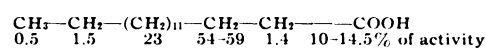
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in the 6 position was oxidized more slowly than that labeled in the carboxy group. Moreover, isolation of the palmitic and stearic acids from the rats revealed that the palmitic acid from the rats receiving the 6-labeled stearic acid was indeed active, although only one-twelfth as active as the C<sub>18</sub> acids from the same animals. Thus it appears that in the oxidation of stearic acid, appreciable numbers of molecules escape at the C<sub>16</sub> stage and mix with the body pools of palmitic acid.

The reverse reaction, conversion of palmitic to stearic acid, has also been shown to occur. In experiments concerning the mechanism of carbohydrate sparing of fatty acid oxidation, Losso *v* and Chaikoff<sup>7</sup> found that although most of injected palmitic acid was stored as such, some appeared in the C<sub>18</sub> acids, especially in fed as compared with fasted rats. Since the carboxy carbon of the stearic acid contained only 2 per cent of the activity, it appeared that the activity was incorporated largely as palmitic acid rather than by total synthesis from acetate. These conclusions had been reached previously by others. Zabin,<sup>8</sup> using rat liver slices or intact rats, studied the incorporation of carboxy-labeled acetate into the saturated fatty acids of the livers. The activity of the carboxy group and of the last two carbons of the saturated fatty acids was checked in palmitic and stearic acids separated by distillation of the methyl esters. In the case of the fed animal, it was found that the activity from the acetate was distributed evenly throughout the palmitic acid chain. In the fasted animal or in liver slice experiments, however, the carboxy groups were several times more active than the average of the remaining carbons. Since most of the activity in the stearic acid was found in the carboxy group, it again appeared that this acid was formed largely by elongation of palmitic acid. This hypothesis has been confirmed by Lipsky, Haavik, Hopper and McDivitt,<sup>9</sup> who found that in the plasma of patients injected with acetate-1-C<sup>14</sup> the peak activity appeared first in the palmitic acid and was followed by the peak in stearic acid.

That palmitic and higher acids can be formed from the lower acids has been shown by Anker.<sup>10</sup> Rats on a fat-free diet were fed 35 mg per day

of myristic acid-1-C<sup>14</sup> for three days and were then killed for extraction of total fatty acids. These were separated into saturated and unsaturated fractions by the lead salt technic. The methyl esters of the saturated and the hydrogenated unsaturated acids were fractionally distilled and were degraded stepwise by the Borodin (silver salt bromination) reaction. In the case of palmitic acid, the degradation was carried out for three steps and the last two carbons were also isolated as acetic acid by chromic acid oxidation. The results obtained can be represented as follows:



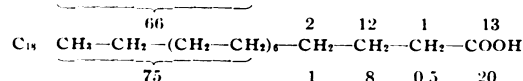
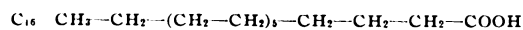
Since the third carbon is considerably more active than any of the others, it is evident that it is derived from the carboxy group of myristic acid. The remainder of the chain is active by virtue of total synthesis of palmitic acid from diluted active acetate. It is noteworthy first, that the last two carbon atoms may not be as active as the average of the last 13, and second that there is considerable activity in the even carbon atoms. This latter activity may very well be an artifact due to overoxidation during the degradation procedure.

From the unsaturated acids were obtained, after hydrogenation, myristic acid (evidently from myristoleic) with most of the activity in the carboxy group, and stearic acid (evidently from oleic and linoleic acids) with 7-10 per cent of the total isotope in the carboxy group. From these data, it appears that carbon atoms 5 to 18 of the oleic acid were derived from myristic acid to which two acetate residues were added. As will be seen below, it is most likely that the oleic acid was formed by dehydrogenation of stearic acid containing this distribution of isotope.

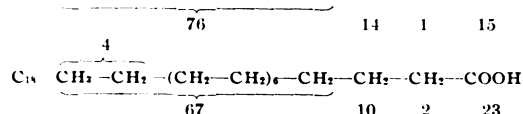
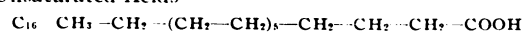
The distribution of activity in fatty acids synthesized from 1-C<sup>14</sup>-acetate by the intact mouse was investigated by Dauben, Hoerger and Petersen.<sup>11</sup> Four hours after subcutaneous injection of the active sodium acetate, the mice were killed and the fatty acids were isolated from the saponified carcasses and separated by fractional distillation of their methyl esters. The unsaturated fraction separated by the lead salt technic, was hydrogenated prior to distilla-

tion. Each fatty acid was then degraded stepwise, and the activity of the first three or four carbon atoms was assayed. In some cases, the last two carbons were also obtained for counting by oxidation with chromic oxide. Following are the results obtained, expressed as per cent of total activity for each carbon atom or group of carbon atoms:

## Saturated Acids



## Unsaturated Acids



These results confirm the previous evidence that palmitic acid is totally synthesized from acetate, since the first and third carbons have approximately the same activity. However, the carboxy group of the stearic acid is approximately three times as active as the third carbon, confirming the hypothesis that stearic acid is synthesized to a great extent by elongation of palmitic acid.

In these experiments, as in those of Anker,<sup>10</sup> the distribution of activity in the unsaturated fatty acids closely corresponded to that of the saturated acids of the same chain length. This, together with their lower total activity would indicate that the unsaturated fatty acids are formed from the corresponding saturated acids by direct dehydrogenation. These ideas are supported by the experiments of Lipsky and his co-workers,<sup>9</sup> who found that in the serum of patients injected with radioactive acetate, the peak of activity of oleic acid followed that of stearic acid. Mead and Howton<sup>12</sup> also found that after the feeding of  $\gamma$ -linolenic acid (6,9,12-octadecatrienoic acid) to rats, the oleic and palmitoleic acids isolated from their organs and depot fat after four hours had one-seventh and one-fourth the activity respectively of the corresponding saturated acids. The indication, then, is that the saturated fatty acids are not formed by hydrogenation of the unsaturated acids, but that the reverse reaction is the normal mechanism for production of the monounsaturated fatty acids.

This probability makes likely the modification (Fig. 1) of Schoenheimer's original scheme for interconversion.

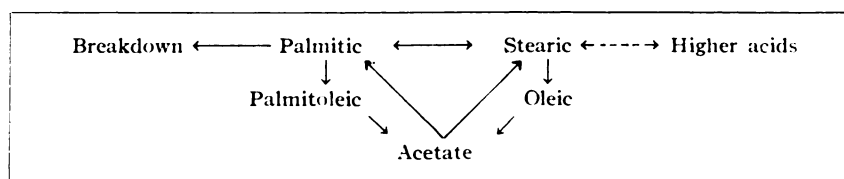


Fig. 1

Oxidation of the residual fatty acid from stepwise degradation of the 18-carbon unsaturated acids revealed only 4 per cent of the total activity in the last two carbons rather than a calculated 9 per cent. This is in agreement with the results of Anker<sup>10</sup> and may indicate that a process other than direct synthesis of palmitic acid from acetate can occur. As will be seen below, it is possible that formed acids can be partially degraded to all stages and rebuilt with active acetate. This would result in a slightly decreasing activity in the odd carbon atoms proceeding toward the terminal methyl groups. This process, then, would modify the more usual total synthesis and degradation of the 16-carbon acids.

## SUMMARY

It appears that palmitic acid is largely synthesized or broken down with little formation of intermediate chain-length acids, but that this process can and does occur to a slight extent. Stearic acid is synthesized largely by elongation of palmitic acid and is partially degraded by removal of 2 carbons to form this acid. Palmitic and stearic acids can be dehydrogenated to the monounsaturated acids, palmitoleic and oleic, which are probably largely formed by this process. The reverse reaction, hydrogenation of the unsaturated to the saturated acids, however, probably does not appear to occur to any extent.

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