FAT METABOLISM

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According to Voit, a man ingests as a part of his food an average of 56 grams of fat per day. Assuming this average to be correct and allowing for a lower consumption during infancy and childhood, we find that when a man reaches the age of forty he will have eaten approximately 700 kg. of fat, the energy value of which is nearly 6½ millions of large calories. This is equivalent to approximately 2.7×10^{16} ergs or 2.6×10^{9} kilogram-meters. It is, however, less than 20% of the total energy intake.

The tissues of an adult human contain relatively constant amounts of protein and carbohydrate. Their fat content, on the other hand, may vary within wide limits depending upon many factors.

Two main classes of fatty substances are found in animal tissues. Under the French classification these have been designated as the 'element variable' which is made up of true fats and oils, chemically glycerides of fatty acids, and the 'element constant,' consisting of such complex compounds as lecithin, cerebrosides, lipo-proteins and the like. The amounts of the former class of compounds found in the tissues vary widely with different individuals; in starvation these compounds are readily mobilized and used as sources of energy. Substances in the latter class occur in relatively constant amounts in tissues; in starvation they resist the forces of mobilization. From a functional standpoint, the latter are undoubtedly far the more important.

The most characteristic part of the lipid (or fat) molecule is its fatty acid. In order to show more clearly the numerous fatty acids which occur in the food, most of which may enter the body tissues if this food is eaten when body fat is being stored, there is grouped in Table I a list of the "food fatty acids."

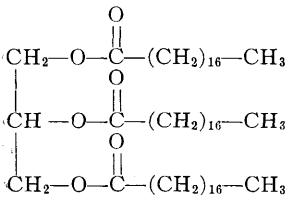
TABLE I.

THE FATTY ACIDS WHICH OCCUR IN FOODS.

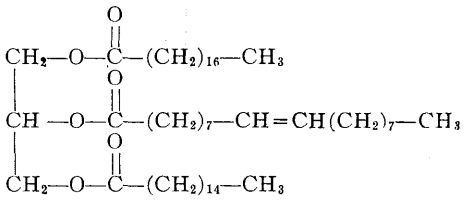
Name of Acid	Formula	No. of HC=CH	Mol. Wt.	Iodine No.	Typical Occurrence in Foods
Butyric	$C_4H_8O_2$	0	88	0	Butter
Caproic	$C_6H_{12}O_2$	0	116	0	Butter
Caprylic	$C_8H_{16}O_2$	0	144	0	Butter, cocoanut oil
Capric	$C_{10}H_{20}O_2$	0	172	0	Butter, cocoanut oil
Lauric	$C_{12}H_{24}O_2$	0	200	0	Butter, cocoanut oil
Myristic	$C_{14}H_{28}O_2$	0	228	0	Butter, nutmeg fat
Tetradecenoic	$C_{14}H_{26}O_2$	1	226	112	Fish oils
Palmitic	$C_{16}H_{32}O_2$	0	256	0	All fats and oils
Hexadecenoic	$C_{16}H_{30}O_2$	1	254	100	Peanut oil, fish oils
Hexadecatrienoic	$C_{16}H_{26}O_2$	3	250	305	Fish oils
Stearic	$C_{18}H_{36}O_2$	0	284	0	Tallow, lard
Oleic	$C_{18}H_{34}O_2$	1	282	90	All fats and oils
Linolic	$C_{18}H_{32}O_2$	2	280	181	Animal lipids, semi-drying oils
Linolenic	$C_{18}H_{30}O_2$	3	278	274	Rarely in foods
Clupanodonic	$C_{18}H_{28}O_2$	4	276	368	Fish oils
Arachidic	$C_{20}H_{40}O_2$	0	312	0	Peanut oil
Gadoleic	$C_{20}H_{38}O_2$	1	310	82	Fish oils
Arachidonic	$C_{20}H_{32}O_2$	4	304	334	Animal lipids, fish oils
Eicosapentenoic	$C_{20}H_{30}O_2$	5	302	420	Fish oils
Docosatetrenoic	$C_{22}H_{36}O_2$	4	332	306	Brain lipids, fish oils
Docosapentenoic*	$C_{22}H_{34}O_2$	5	330	385	Brain lipids, fish oils
Docosahexenoic	$C_{22}H_{32}O_2$	6	328	464	Fish oils
Tetracosanoic	$C_{24}H_{48}O_2$	0	368	0	Brain lipids

*Tsujimoto prefers to designate this acid as clupanodonic (13).

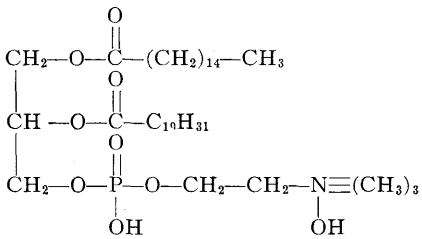
One interesting observation that may be made concerning these fatty acids is that each of them has an even number of carbon atoms. Further, all members of the series of saturated acids from four to twenty-four carbon atoms occur. The unsaturated acids include those of fourteen to twenty-two carbon atoms and of one to six double bonds. The formulae of a number of typical lipids follow:



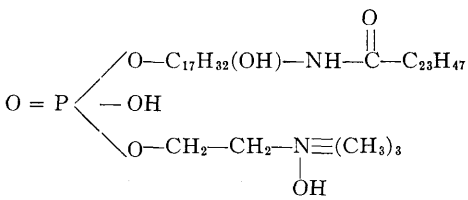
TRISTEARIN.



PALMITO-OLEO-STEARIN.



PALMITYL-ARACHIDONYL-LECITHIN.



SPHINGOMYELIN.

Although there are more than twenty fatty acids occurring in the foods we eat, the common animal body fats are composed chiefly of the glycerides of palmitic, stearic and oleic acids, and in addition generally small amounts of myristic and linolic acids; and less frequently traces of arachidonic. The animal phosphatides usually contain relatively large amounts of more highly unsaturated acids, such as arachidonic. The special function of these phosphatides may be connected in some way with their high unsaturation.

It is worth while to note here two fats which are exceptionally complex—butter fat, which contains at least eleven fatty acids, mostly saturated, and the fish oils which contain even a larger number of acids, most of them with three or more double bonds. Many speculations have been made in unsuccessful attempts to explain the complexity of these fats.

The vegetable fats and oils which are ordinarily used as foods are composed chiefly of palmitic, stearic, oleic and linolic acids. Vegetable foods are relatively low in phospho-lipids.

DIGESTION OF FATS.

Digestion of fats consists of adding the elements of water to form glycerol and fatty acids. This process begins to a very minor extent in the stomach. It is now generally recognized that a fat-splitting enzyme occurs in the gastric juice (1). Although the strong acidity and other conditions in the stomach are not favorable to the action of lipase, there does occur a certain degree of hydrolysis, especially if the fat reaches the stomach in an emulsified condition. As the food passes into the duodenum, however, the conditions change rapidly to those more favorable for saponification. The mildly alkaline juices of the intestine and pancreas and the bile rapidly neutralize the hydrocholric acid. The bile furnishes the sodium salts of glycocholic and taurocholic acid which facilitate emulsification. The intestine and pancreas secrete lipases which act rapidly on the fat as it becomes emulsified. In a relatively short time, therefore, the food fats are changed into glycerol and fatty acids. In the older treatises on digestion this reaction was explained on the basis of the formation of soaps. This appeared necessary to account for the fact that the fatty acids, which are insoluble in water, remain in solution in the digestive juices. Such a conclusion has been criticized in view of the observation that the pH of the intestine is perhaps as often below 7.0 as above; in fact it has been reported as low as 6.0. Theoretically, soaps would be completely hydrolysed and could not exist at this pH. This anomaly has been explained by the work of Verzar and Kuthy (2), who found that the bile salts will dissolve fatty acids with the formation of clear solutions even at pH 6.2.

Reference should be made at this point to the so-called "digestibility" of fats. By this is meant the extent to which fat is digested and absorbed. Earlier work had shown that if a given amount of fat were fed, approximately 90–98% of it was absorbed, the remainder being excreted. In such experiments the fecal fat was determined and estimated as unabsorbed fat. Sperry and Bloor (3), however, found that on a fat-free diet lipids continued to be excreted and, further, the character of this excretion was relatively little affected in amount or kind of fatty acids by food fat. Apparently, therefore, the normal intestine secretes certain lipids constantly. Allowing for this excretion one may infer that when any normal amount of fat is eaten, it is nearly quantitatively utilized. Exceptions to this

statement may be observed when unusually hard fats or fatty acids are fed, such as stearin or stearic acid. These do not melt at body temperature and are very imperfectly absorbed.

ABSORPTION OF FATS.

For many years it has been quite generally believed that the chief path of fat absorption was through the lacteals and lymph vessels of the intestine. The bile salts are indispensible carriers in this process. By holding the fatty acids in solution they favor diffusion through the cells and into the lymph vessels. Thence they are transported as neutral fat to the thoracic duct which empties into the left subclavian vein. The bile salts pass again into the liver which resecretes them into the bile. In this way they go through a continuous cycle of activity. Should this cycle be interrupted by obstruction of the bile duct or by artificial drainage of the bile out of the body following operations on the gall bladder, fat absorption fails. Certain definite digestive disorders are then manifested, the most important of which is the appearance of large quantities of fatty acids in the stools.

Although it is generally agreed at present that the principal path of fat absorption, at least up to 60%, is that just described, recent investigations (4) are leading to the belief that most of the remaining 40% passes into the portal blood. An appreciable lipemia has been described in portal blood during active fat absorption.

A number of important facts about the mechanism of fat absorption are now available.

(1) The fatty acids appear as neutral fats in the lymph. This change from the products of saponification in the intestine involves recombination in glyceride form. It is possible that lipases catalyse both processes. In this synthesis the bile salts probably are set free.

(2) Even if fatty acids or ethyl esters are fed, neutral fat appears in the lymph. Glycerol, therefore, is supplied in the process, either by direct synthesis or from the blood.

(3) The character of the fat appearing in the lymph represents an average between the food fat and endogenous fat. In this connection it should be mentioned that if endogenous fatty acids appear here, the 60% which can be recovered from the lymph is composed of fatty acids from the two sources; actually, therefore, less than 60% of the food fat can be recovered in the lymph.

(4) If a very finely divided emulsion of fat and mineral oil is fed, the former is almost quantitatively and selectively absorbed leaving the mineral oil behind to a degree equally quantitative. The process is, therefore, quite a specific one.

The question may well be asked "why are fats hydrolysed in the intestine only to be resynthesized before appearing in the blood?" Of course this can not be answered positively. Leathes (5) has suggested that by this process of recombination glycerides of different structure may be produced—in other words new fats more characteristic of the new organism. May there not be, therefore, some analogy between fat absorption and resynthesis and protein absorption and resynthesis? The building stones which occur in combined form in the foods are thus liberated by digestion and recombined in the new organism to form compounds characteristic of and perhaps essential to that organism.

Although small amounts of free fatty acids may be found in the blood, they occur in this fluid chiefly combined as neutral fat, phospho-lipid and cholesterol esters. Since these are insoluble in water and serum, they are carried, both by serum and cells, as an emulsion of finely divided droplets. During absorption the serum may actually be milky in appearance due to its fat content.

Following absorption fat may pass to the liver or the tissues, depending on whether it has entered the portal or systemic blood. In consequence of this, three well recognized types of transformations may occur: changes in the liver; oxidation; deposition as body fat.

THE ACTION OF LIVER CELLS ON FAT.

The normal liver contains 5% lipids, about evenly distributed as phospho-lipid and neutral fat. In 1909 Leathes and Wedell (6) showed that when cats are fed on certain fats the iodine number of the liver fatty acids is greater than that of the fatty acids of the food. Leathes suggested, on the basis of these and other results, that liver cells have the property of introducing double bonds into (desaturating) fatty acids, thus making them more reactive so that they are more easily oxidized in the tissues. Thus from stearic acid, oleic acid (or iso-oleic) would be formed; from oleic there would result linolic. Space will not permit adequate discussion of this "desaturation theory."

Suffice to say, the phenomenon of increased unsaturation may be explained on the basis of selective deposition of certain highly unsaturated acids which occurred in the oils which Leathes fed. The liver is unusually rich in phospholipids which seem to attract specifically acids of high unsaturation. The validity of the theory has been further criticized since the discovery of arachidonic acid ($C_{20}H_{32}O_2$) in the liver by Hartley (25), subsequently confirmed by Levene and Simms (7), Brown (8), Klenk and Schoenebeck (9) and very recently by Bloor and Snider (10). This highly unsaturated acid of twenty carbon atoms and four double bonds occurs in considerable amount in the liver (as high as 12% of the total fatty acids) (11). If this acid had originated by desaturation of C_{20} fatty acids, one would have to account for these acids in the food. Moreover, by desaturation one would expect to find C_{20} acids of one, two, three and four double bonds; the last, however, is the only one known to occur. Very recent reports (9) are to the effect that under certain conditions C_{22} acids with five bonds occur in the liver. Actually, the content of C_{20} and C_{22} acids in ordinary food fats is quite insignificant. It would appear more reasonable, therefore, to assume that highly unsaturated acids result from some other obscure process, probably synthetic in nature. The writer considers the evidence for desaturation as quite unsatisfactory, although, of course it has not been disproved.

Whether the fatty acids are desaturated in the liver or not, certain observations point to very active fat metabolism in this organ. Experiments have shown that liver fat changes rapidly. In starvation, for example (12), increased amounts of body fat are rapidly mobilized into the liver. Variations in food fat are rapidly reflected in the character of liver fat. Further, in certain pathological conditions such as acute yellow atrophy and miliary tuberculosis the liver may contain as much as 50% of lipids, mostly neutral fat, so that the ratio of neutral fat to phospho-lipids increases from a normal of about 1.0 to one has high as 71 (11). The forces which attract fat to this organ in such large amounts are obscure, although the abnormality may lie not in unusual attraction but in liver hypofunction—a failure of fat to be used in liver tissue. Thus fat may be attracted to liver cells by normal forces; then due to failure of liver function it remains there.

OXIDATION OF FAT.

The fat which has been absorbed into the blood and which may have passed through the liver changed or unchanged is transported to the various tissues where it may be either oxidized or stored according to the balance of supply and demand of energy available and required by the tissue cells. The forces which come into play at this point are entirely obscure; the effect of the glands of internal secretion, however, is recognized.

If fat is oxidized, we do not know as yet whether this happens to the fat molecule as a whole or whether hydrolysis precedes oxidation. In any case it is quite certain that the glycerol follows one course of degradation, and the fatty acids another.

TABLE II.

FATE OF PHENYL FATTY ACIDS FED TO DOGS.

ACID	FORMULA	EXCRETED IN URINE (Conjugated)
Benzoic	C_6H_5COOH	C_6H_5COOH
Phenylacetic	$C_6H_5CH_2COOH$	$C_6H_5CH_2COOH$
Phenylpropionic	$C_6H_5CH_2CH_2COOH$	C_6H_5COOH
Phenylbutyric	$C_6H_5CH_2CH_2CH_2COOH$	$C_6H_5CH_2COOH$
Phenylvaleric	$C_6H_5CH_2CH_2CH_2CH_2COOH$	C_6H_5COOH

(Knoop)

The classic researches of Knoop were the first to give us a clear picture of the mechanism of the oxidation of the fatty acids. From the standpoint of their chemical properties it would be expected that these acids would be attacked either on the alpha carbon atom or at a double bond. Apparently, however, in living cells the point of attack is the beta carbon atom. Knoop (14) fed to dogs phenyl derivatives of the lower fatty acids noting how they were excreted, the results of which are given in Table II.

Benzoic and phenyl acetic acids are excreted in combined form in the urine, both groups being resistant to oxidation. Phenyl propionic and valeric acids are likewise excreted as benzoic, whereas phenyl butyric appears as phenyl acetic. These results support the so-called beta-oxidation theory, which is outlined in Figure 1.

It is apparent from this outline that the normal course of oxidation is a succession of cycles involving the loss of one molecule of acetic acid (two carbon atoms) at the end of each cycle. The final product, therefore, is acetic acid which

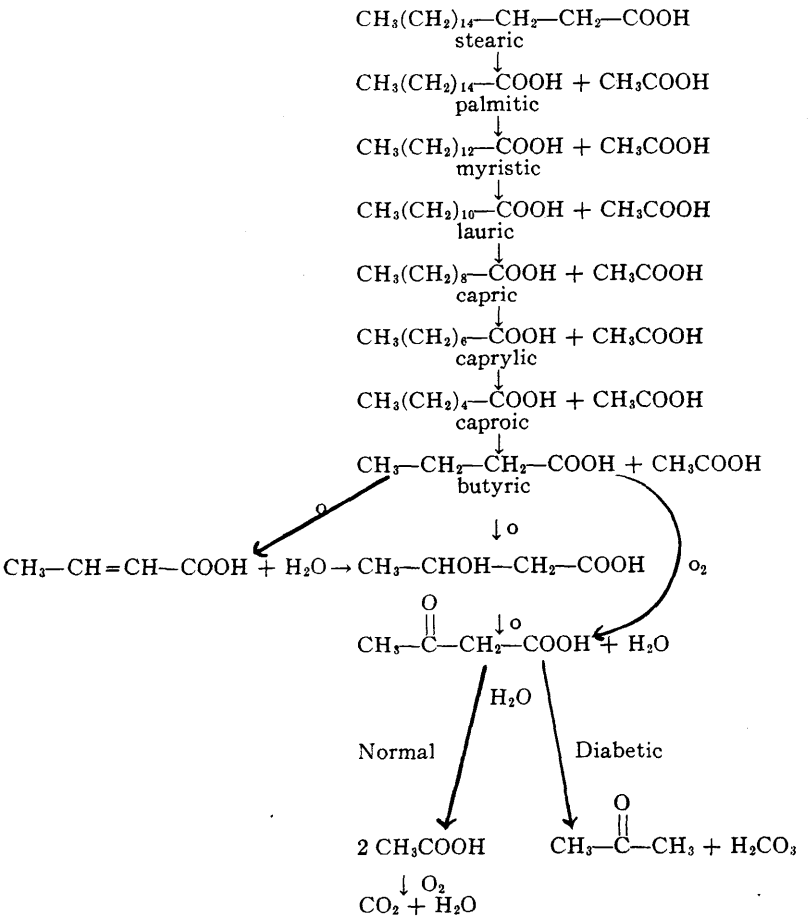


FIGURE 1.

BETA-OXIDATION OF STEARIC ACID.

eventually oxidizes to carbon dioxide and water. It is now well recognized that an intermediate of carbohydrate metabolism is essential to the completion of this process; in its absence, instead of acetic acid, other incomplete oxidation products appear, the so-called acetone bodies. Such a condition exists in diabetes.

This disease apparently results from hypofunction of the pancreas, which fails to supply adequate amounts of insulin. As the supply of insulin diminishes, less and less carbohydrate is oxidized. The substance necessary for final oxidation of the derivatives of butyric acid is no longer available. Ketogenesis results. So long, however, as there is a proper balance between sugar oxidation and fat oxidation (antiketogenesis) butyric acid is converted quantitatively into acetic acid. In the early stages of diabetes there may be enough insulin to prevent ketone formation, but not enough to prevent excretion of sugar in the urine. Ketogenesis appears only in the later and more severe stages of the disease. It is finally accompanied by severe and terminal acidosis. When the acidosis is relieved by administration of glucose and the missing intermediate is supplied by combined administration of glucose and insulin, the situation in most cases is rapidly relieved.

Aside from the evidence furnished by Knoop and by the metabolism in diabetes four other investigations serve to confirm the beta-oxidation theory:

(1) The observation of Dakin (15) that when phenyl propionic acid is fed to dogs, the intermediates predicted from the theory, phenyl-beta-hydroxypropionic acid, benzoyl acetic and acetophenone as well as hippuric acid could be detected in the urine.

(2) Dakin's discovery (16) of the analogous in vitro reaction whereby soaps may be oxidized on the beta-carbon atom by hydrogen peroxide.

(3) Embden and co-workers' experiments (17) showing that when soaps of even carbon acids were perfused through the surviving liver, acetone appeared in the blood; when soaps of odd carbon acids were perfused, no acetone was formed.

(4) The discovery by Kahn (18) that when synthetic fats with an odd number of carbon atoms were fed to diabetics, little or no acetone bodies resulted.

Beta-oxidation explains well the oxidation of the saturated acids, but how about the unsaturated acids? Oleic acid, for example, with a double bond between the ninth and tenth carbon atoms, should be more easily attacked by oxygen than stearic. In the body, however, this apparently is not true. What information is available appears to show that oleic acid, and in fact the other unsaturated acids, likewise oxidize on the beta-carbon atom. Certain of the tissues, such as the liver,

suprarenal, spleen, and brain, concentrate acids with as many as four and five double bonds. Instead of being easily oxidized, these seem to be unusually stable during life.

To summarize the oxidation of fats, therefore, it may be said that these are probably first hydrolysed into glycerol and fatty acids, the former oxidizing similar to the carbohydrates and the latter by series of beta-oxidation cycles. As a summation of this process in the normal individual a gram of average fat yields a little over nine kilogram calories of heat.

THE SYNTHESIS AND STORAGE OF BODY FAT.

We have now to consider the formation and deposition of body fat. If the energy value of the food intake exceeds that required by the body, fat is stored. This may result by synthesis either from preformed fatty acids furnished by the food or by the generation of fatty acids from carbohydrate (and indirectly from protein). Both processes are important although little is known about them. What metabolic force, for example, determines whether a fatty acid molecule is burned or stored? If burned, does this happen in the cells of the liver, in the blood cells, or in certain tissue cells? How does an excess of total energy for the organism as a whole bring about synthesis of fat from carbohydrate?

Body or depot fat may be synthesized from carbohydrates by reduction of the latter and liberation of oxygen; a speculative equation for this process follows:

$$19\ C_6H_{12}O_6 = 2\ \begin{array}{l} CH_2-O-\overset{\overset{O}{\|}}{C}-(CH_2)_{16}-CH_3 \\ | \\ CH-O-\overset{\overset{O}{\|}}{C}-(CH_2)_{16}-CH_3 \\ | \\ CH_2-O-\overset{\overset{O}{\|}}{C}-(CH_2)_{16}-CH_3 \end{array} + 4\ H_2O + 52\ O_2$$

From this equation it will be observed that from 100 gm. of glucose about 48 grams of tristearin and 47 grams of oxygen will result. Since this oxygen is endogenous, less oxygen from the air is required for respiration when fat is being synthesized by such a process, resulting in an apparent rise in the respiratory quotient. Under ordinary conditions in normal human beings the effect on the R. Q. would be slight, but in certain animals and fowls whose metabolisms are inherently fat-forming, such

as hogs and geese, if ample food is given, fat synthesis from carbohydrate causes a decided rise in R. Q. Bleibtreu (19), for example, showed that geese during luxus feeding gave respiratory quotients as high as 1.33. On starving these fattened fowls, this fell to as low as 0.72, showing that fat was being burned almost exclusively. Pembrey (20) found that marmots before hibernation eat excessive amounts of carbohydrates which are converted into and stored as fat and used during the hibernation period.

The chemical composition of stored fat is dependent on fatty acids of both endogenous and exogenous origin. Regarding the latter numerous investigations have shown that almost any of the higher fatty acids may pass into body fat, if they are eaten and absorbed at a time when fat is being stored. These include the acids which are known to be synthesized from carbohydrate, namely palmitic, oleic and stearic (and probably linolic) and in addition such common acids as myristic, linolic, linolenic, lauric, the highly unsaturated acids found in phospholipids and fish oils, arachidic and the like. In addition certain unusual fatty acids such as those which have been treated with bromine and iodine, erucic acid and chaulmoogric, when fed, are absorbed and deposited. In the case of chaulmoogric acid, the depot fat is optically active (11).

Many of these unusual acids have likewise been shown to pass into milk fat; hence they may be found in the butter fat of animals which have eaten them.

Investigations during the past few years by Eckstein (21), Powell (22) and Davis (23), have brought out the fact that certain of the acids of lower molecular weight, from C_4—C_{10} inclusive, do not appear in the depot fat; they are either completely oxidized or serve to synthesize higher fatty acids.

THE ESSENTIAL NATURE OF FATTY ACIDS.

Until quite recently fats have not been considered to be an essential dietary constituent. In (1929), however, Burr and Burr (24) described certain abnormalities in rats fed on a diet practically free from fatty acids, and believed to supply all other known dietary essentials. One of the outstanding manifestations of this condition was a dermatitis, especially noticeable on the tails. Linolic acid was found to be curative. While certain other investigators have disputed these results, they are especially interesting since they open up an entirely

new field of nutritional investigation. The future may disclose other essential functions of certain fatty acids.

On account of the limitations of space a more detailed discussion of the various factors related to fat metabolism has been impossible. There are obviously many gaps in our information on this subject. Only facts that are now generally recognized have been included. Future research on the fats and oils and especially study of that complex group called the phospholipids will not only give us a clearer picture of the details of fat transformations in cells but will disclose, no doubt, many new and important functions of these substances in living processes.

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Mosquitoes.

An addition to the taxonomic treatment of all the species of mosquitoes known to occur in N. A. A large amount of discussion is given on structures, biology, ecology, disease, transmission and methods of control. It is especially valuable for those interested in fresh water biology, public health work or medical entomology and can be used extensively in local areas for the study of mosquito problems.—D. M. DeLong.

A Handbook of the Mosquitoes of North America, by Robert Matheson. xviii+274 pp. Springfield, Charles C. Thomas. 1933.