The lore of lipids

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In this Silver Anniversary Issue of the *Journal of Lipid Research* there are articles that review important recent developments in various areas of lipid research. These reviews not only summarize the state of knowledge in 1984, but they point the way to new avenues of research. Other articles in this issue are more retrospective; they call attention to what was known in particular areas of lipid research 25 years ago, and summarize the progress made since then. This review is an assembly of some well known and little known facts and fables about fats, lipids, and research, some of which go back further than 25 or 100 years. Some of the material may be of only passing interest in the history of the science of lipids, but the review also covers some old but significant scientific endeavors that had profound effects on the development of modern chemistry and physiology. This article might very well be subtitled "A Retrospective Pursuit of Lipid Trivia."

Lipoid, lipin, lipide, lipid

The first issue of the *Journal of Lipid Research* contained an editorial (1) in which Dr. J. H. Bragdon commented on the use of the term "lipid" instead of "lipide" in the name of the *Journal*. This was not a trivial issue in 1959. Bragdon pointed out that ". . . a few journals have for some years insisted that the proper spelling of the word is 'lipide'." Indeed, in 1952 Patterson (2) made a strong case for the term "lipide," and even wrote, "Pronounce -ide, by the way, as in ride, not as in rid."

Actually four different terms have been used to designate the class of naturally occurring substances that we now refer to as lipids, and at times there was apparently some confusion over which word was the most suitable. The word "lipoid," meaning resembling fat, was first used (according to the 1933 edition of the Oxford English Dictionary) in 1876, and it was in common use (as both an adjective and noun) in the early part of this century, as judged by the indexes in the first volume of *Chemical Abstracts* in 1907. It did not appear in the index of the *Journal of Biological Chemistry* until 1915, although it was used earlier in a few papers.

In 1910, the word "lipine" was used to "denote compounds of fatty acids containing nitrogen but no phosphorus or carbohydrate group." The word "lipin" was proposed as a generic name for fats and fat-like substances (lipoids) in 1912 (3). Terms such as phospholipins, glycolipins, glycophospholipins, and sterins were suggested. In that year it also made its first appearance in the *Journal of Biological Chemistry* in volume 13 (4). Interestingly, the author of this paper was one of the coauthors of the paper that advocated the use of "lipin." However, this term did not have a significant impact. It was last listed in the *Journal of Biological Chemistry* index in 1915.

In 1920 Dr. W. R. Bloor (at the University of Rochester) commented on the fact that, at a meeting of the American Society of Biological Chemists in the previous year, it was decided that the available information on the classification of the fats and related substances was insufficient to justify a classification at that time (5). Nevertheless, Bloor felt that it was useful to attempt such a classification, and the one that was published proposed three groups: simple lipoids (fats and waxes), compound lipoids (phospholipoids, glycolipoids), and derived lipoids (fatty acids and sterols and fatty alcohols). He wrote ". . . they [lipoids] should be considered together, and when so considered they form a group which is believed to be as distinct and well-defined as that of the carbohydrates and proteins." Five years later in 1925, Bloor published a comprehensive review on the biochemistry of the fats (6). He presented a modified classification in which the word "lipide" was used. "Lipoid" was dropped because that term was understood by many investigators to exclude the fats (i.e., esters of the fatty acids with glycerol). The term "lipide" had been introduced by M. Gabriel Bertrand in 1923 (7) (along with "glucide" and "protide") and the proposals were adopted by the International Union of Pure and Applied Chemistry. The word "lipid" may have first appeared in the *Journal of Biological Chemistry* in 1926 in a paper by Warren M. Sperry (8). The material in this paper was taken in part from Sperry's Doctor of Philosophy thesis at the University of Rochester. In a footnote Sperry wrote "The term 'lipid' is used in accordance with the recommendation of the International Congress of Pure and Applied

Chemistry." However, there was opposition to the proposals of Bertrand, and the IUPAC in 1930 declared that the adoption was not definitive. "Lipoid" was a main subject heading in *Chemical Abstracts* until 1936, when it was replaced by "lipide." In the *Journal of Biological Chemistry* "lipid" was most frequently used in articles and indexes from the time of Sperry's paper in 1926 through 1945, although "lipoid" persisted until 1939. Inexplicably, in 1946, "lipid" was replaced by "lipide" in titles of papers and in the indexes of the *Journal of Biological Chemistry.* Thus when the first issue of the *Journal of Lipid Research* appeared in 1959, "lipide" was the accepted terminology in at least two important publications in the United States.[1]

The *Journal of Lipid Research* was one of the first subspecialty journals, and certainly the first to use the word "lipid" in the name of a journal. It is significant, and perhaps more than a coincidence, that after the appearance of the first issue in October of 1959, the word "lipide" was abandoned by the *Journal of Biological Chemistry* (in 1960) and by *Chemical Abstracts* (in 1962).

The etymology of "lipid" and "fat"

By the late 1860's there was enough general knowledge about carbohydrates and proteins for these substances to be given the names "carbohydrate" and "protein", respectively. The earliest use of the word carbohydrate was in 1869. One year earlier, the Dutch chemist, G. J. Mulder invented the word "protein", derived from the Greek word πρωτεῖος, meaning primary or prime. Mulder regarded "residual substances obtained from casein, etc. . . . as the essential constituent of organized bodies" (Oxford Universal Dictionary, 1955). "Carbohydrate" and "protein" are words invented to describe a particular property of each of these substances. Although "lipoid" is also an invented word, the root "lipo-" is derived from the Greek noun λίπος, meaning fat. Perhaps the earliest use of this root in a word that is related to fat is in "lipoma", first used in 1830. "Lipohaemia" was used by Thudicum in 1872. "Lipogenesis" was first used in 1882, and the word "lipase" was used in 1897.

The ancient Greeks had many words for fat. For example, στέαρ (stear) hard fat, tallow, suet; πῖαρ (piar) fat, tallow, suet; πῖμελή (pimele) fat; λίπος (lipos) animal or vegetable fat; δημὸς (demos) fat; ἔλαιον (elaion) oil. This last word was carried over into the Latin *oleum,* meaning oil or olive oil. Other Latin words are *adeps,* soft fat or grease of animals, suet, lard; *sebum,* hard fat, but also suet or tallow. The Latin adjective *pinguis* is from the Greek adjective παχύs (pakus) meaning fat. This word is the root of numerous Latin words, all pertaining to fat, e.g.: *pingue,* fat or grease; *pinguiculus,* somewhat fat; and *pinguiarius,* one who likes fat. "Pinguis" is the root for words rarely used at present. Many of the early scientific and medical texts were written in Latin (even up to the middle of the 18th century). Thus it is not surprising that Latin words pertaining to fat have found their way into the English language, e.g., pinguid (greasy, oily, unctuous) and pinguescent (becoming fat). We are indeed indebted to that unknown person in the early 19th century who opted for brevity and ease of spelling and pronounciation in using the root word "lipo-" instead of "pingui-". Otherwise we might have had to contend with pinguiproteins, apopinguiproteins, phosphopinguids, glycosphingopinguids, and pinguiphilic.

The word "fat" first appeared in the English language as a noun in 1539, and was defined as the "oily concrete substance of which the fat parts of animal bodies are chiefly composed." The adjective "fat" can be traced back to the Anglo-Saxon word *faett,* the past participle of a word meaning "to fatten". The word can be further traced back through the Latin (*pinguis*) and Greek (παχύs) to a Sanskrit word *payate* meaning "swells, grows, teems, fattens."

Ancient and medieval fats

In ancient times a special importance was given to fats and oils. They were basic necessities of life, important not only as foodstuffs, but as the source of light. The olive was the main source of oil for all classes from the eastern Mediterranean to Spain. Along with other oil-producing plants, e.g., flax, sesame, and poppy, it was cultivated because it provided a larger supply of oil than could be produced through domestication of animals. Olive oil was obtained by twisting a porous bag containing the olive pulp in order to squeeze out the oil. In later technology the lever and screw were used to apply pressure to the bag containing the pulp. In areas where the olive did not flourish, the main source of oil was from the seed of the sesame plant. There is evidence that the Assyrians used a hot water process to obtain the oil. After the seed was crushed, it was treated with boiling water. The oil rose to the surface and was skimmed off; final traces of water were removed in a special vessel with an outlet on the side so that the oil could be separated from the water residue (9).

In the ancient Near East, fat and oil were spiritual symbols. Fat was used in ritual peace offerings, and the Old Testament contains explicit directions as to its use. In the description of the consecration of Aaron and his sons, the following instructions are given: "And thou

[1] The *Journal of Biological Chemistry* and *Chemical Abstracts* are cited because of their importance in biochemical and chemical research in the United States. However, other equally important and long-standing journals (e.g., *Biochemical Journal* and the *American Journal of Physiology*) apparently never used the spelling "lipide."

shalt take all the fat that covereth the inwards, and the lobe above the liver, and the two kidneys and the fat that is upon them, and make them smoke upon the altar" (Exodus 29:13). There was a specific prohibition against consumption of fat of the three sacrificial animals: "Ye shall eat no fat, of ox, or sheep, or goat. And the fat of that which dieth of itself, and the fat of that which is torn of beasts, may be used for any other service; but ye shall in no wise eat of it. For whosoever eateth the fat of the beast, of which men present an offering made by fire unto the Lord, even the soul that eateth it shall be cut off from his people" (Leviticus 7:23–25). The Old Testament writers anticipated by more than 2000 years what is advocated by many present day doctors and nutritionists in regard to the consumption of saturated fat. Throughout the Old Testament oil was used for anointing. Moses was instructed in a most explicit manner as to how the anointing oil was to be made from olive oil and a variety of spices (Exodus 30:22–25).

The application of a holy oil was believed to impart directly a portion of the divine spirit. In some societies the intention of the anointing was to impart to the anointed the qualities of the totem animal. Sir James George Frazer in *The Golden Bough* cites a number of strange uses of fat (10). For example, lion fat inspires a man with boldness; and the fat of crocodiles or venomous snakes applied to the hair is very efficacious for women whose hair is thinning. At various times and places, magical and curative properties have been ascribed to fats and oils. Some interesting examples are found in Umberto Eco's recent book, *The Name of the Rose*, a "detective story" of the late Middle Ages set in the year 1327. The following passage is spoken by one of the monks (11):

"There was a book of secrets written, I believe, by Albertus Magnus; I was attracted by some of the curious illustrations, and I read some pages about how you can grease the wick of an oil lamp, and the fumes produced then provoke visions." "You know, if you take the wax from a dog's ear and grease a wick, anyone breathing the smoke of that lamp will believe he has a dog's head, and if he is with someone else, the other will see a dog's head. And there is another unguent that makes those near the lamp feel as big as elephants. And with the eyes of a bat and of two fish, whose names I cannot recall, and the venom of a wolf, you make a wick that, as it burns, will cause you to see the animals whose fat you have taken. And with a lizard's tail you make everything around you seem of silver, and with the fat of a black snake and a scrap of a shroud, the room will appear filled with serpents."

Medieval European pharmacopeias contained fascinating cures and remedies, and many were made from fats or oils. For example, the 1677 Pharmacopeia of the College of Physicians in London lists the following (12): hippopotamus fat for the agues (acute fever); the ashes of the skin of a serpent mixed with oil of roses for sores in the ear; oils derived from earthworms, scorpions, puppy dogs, swallows, foxes, and vipers for various disorders. *Oleum Scorpionum* (Oil of Scorpion) made of 30 live scorpions of medium size, was used for treatment of gout. *Oleum Vulpinum* (Oil of Foxes) was regarded as a "healing, comforting, strengthening oil . . . to ease the gout and pains in the joints, and to restore wasted or withered limbs. It is excellent in convulsions and cramps." One recipe for its preparation starts with a disembowelled fox, its body filled with herbs and oils . . . "sow the belly close and with a quick fire roast him and the oyl that droppeth out is a most singular oyl for all palsies and numbness."

Frazer in *The Golden Bough* also noted (13) that the Chinese had regarded the gall bladder as a special seat of courage, and that ingesting the bile of tigers or bears gives courage. He also cites that the Ainu, a primitive people in the Japanese island of Yezo, celebrated a bear-feast. A young bear was captured and nurtured, and when it was grown it was killed in the winter for its liver. It was believed that the liver was an antidote to colic and disorders of the stomach. Dr. Martin C. Carey (Harvard Medical School) has noted that dried black bear's bile appeared in the first officially commissioned pharmocopeia in medical history in 659. The major indications for its use were jaundice and abdominal pain. Black bear bile contains appreciable amounts of ursodeoxycholic acid, a bile acid that has been used in the treatment of gallstones (14).

The medieval Chinese were ahead of their time in other areas of medical preparations. Gwei-Djen and Needham (15) in an article on medieval preparation of urinary steroid hormones described several methods that were in use in 12th century China to make medications from human urine. In one procedure urine (14.5 gallons) was treated with the juice of soap-beans (which contains saponins), and the mixture was stirred "energetically with a bamboo stick hundreds of times." The clear fluid was decanted after the precipitate had settled. Precipitates from ten such preparations were combined and filtered and thoroughly dried. The residue was ground to a fine powder and treated with boiling water. After filtering through paper over a bamboo sieve, the solution was evaporated to dryness, and the treatment with boiling water, etc. was repeated until the precipitate was "white as snow." The solid material was then heated in a tightly sealed earthenware container until the sublimate condensed. The final product was ground and mixed with dates to make small pills. "Thirty pills should be taken daily with warm wine before breakfast." Gwei-Djen and Needham point out that this procedure anticipated by centuries the discovery that digitonin precipitates many sterols quantitatively. They comment on each step of the procedure and speculate that it might indeed have been an empirical method of partial separation of androgens from esterogens.

Perhaps one of the earliest references to the nature of adipose tissue is found in medieval writings. In his *Quaestiones Naturales* (Questions on Nature) Adelard of Bath in the early 12th century had the following to say about the nature of animals (16). "Those animals, therefore, which have a warm stomach digest their food easily. But those whose natures are cold, bring it back again to their mouths, so that there they may be able to soften it more easily by a second chewing. Such are cows, deer, goats and the like kind, which doctors call by the Greek term melancholic. That all of these, moreover, are of a cold nature, although it may be clear to doctors, can thus be shown to you. For on this account, they have harder and more solid fat, which the ordinary person calls tallow. But others, since they are hotter, have softer fat, since it is better digested, which by common usage is called lard."

Albertus Magnus, who was quoted in Umberto Eco's book, was a German scholar of the 13th century, a teacher of Thomas Aquinas, and one of the most famous precursors of modern science in the Middle Ages. He is said to have been the first to isolate arsenic. Albertus experimented with alchemy, and although he suggested the possibility of transmutation of metals, he did not believe that alchemists had found the methods to accomplish this. He also made extensive contributions to the biological sciences. Notwithstanding the superstitions about the burning of animal fats allegedly ascribed to him, Albertus had interesting insights into the experimental process. In his treatise on alchemy, *De Alchemia,* he set forth eight precepts about the practice of alchemy, some of which are quoted below (17).

"The first precept then is that the worker in this art should be silent and secret, and should reveal his secret to no one, that he should offer nothing further in the way of explanation, knowing for certain that if many know he will accomplish nothing which is not divulged, and when it shall have been divulged, it will be reputed a forgery—and so will be in perdition, and the work will remain imperfect."

In the writings of the alchemists there is a common warning to keep experiments secret. Roger Bacon in his *De Mirabili Potestate Artis et Naturae* quotes Aristotle who wrote in his *Liber Secretorum:* "He is a breaker of the heavenly seal who communicates the secrets of Nature and of Art" and "Many evils follow the man who reveals secrets."

The alchemists undoubtedly had reasons to keep their studies secret. A clue may be seen in the following passage from *De Alchemia.* "I who am truly the least of the Philosophers intend to write about the true art for my associates and friends, clearly and infallibly, but however in such manner that seeing, they may not see, and hearing, they may not understand. Wherefore I beg and adjure you, by the Creator of the world, that you hide this book from all stupid persons. To you indeed I will reveal the secret, but from others I conceal the Secret of secrets because of the envy of this noble science. For the stupid despise it because they are not able to grasp it, and thence hold it hateful and believe it not to be possible, and so envy those who work at it and call them forgers. Therefore beware lest you reveal any of our secrets in this operation."

Some of the other precepts of Albertus Magnus may be of interest and significance even today. Readers may draw their own conclusions about these following principles. His fourth precept ". . . is that the worker in this art [alchemy] should be sedulous and frequent in his operations, and should not tire but should persevere to the end. Because, if he should begin and should not persevere, both time and substance would be lost."

"The seventh is that you ought to beware before all else of involving yourself with princes and potentates in any operation; because of two evils, for if you have involved yourself, they inquire after you from time to time and say, 'Master, how do you succeed? When shall we see something good?' and, not being able to wait for the end of the work, they say that it is nothing . . . and then you will have the greatest of annoyance. And if you have obtained a good result, they think to detain you forever and will not allow you to go away, and so you will be ensnared by the words of your own mouth and entangled by your own speeches."

The eighth precept showed that even 13th century research was faced with monetary problems. "The eighth precept is that no one ought to involve himself in these operations who has not abundant funds, at least enough to be able to provide all things which are necessary for the art and in fact all which are useful. And if he has involved himself and funds lack, then the wherewithal and all else is lost."

The beginning of organic chemistry and the chemistry of fats[2]

Ancient peoples used wood ashes and water for washing, and relieved the resultant irritation with fat or oil (18). Pliny, in the first century, described a preparation of tallow and wood ashes used by Germanic tribes to brighten their hair (18). Both of these preparations were not really soap, but, in a sense, represented an in situ saponification process. The origin of soap (as made by the saponification process) is not known with certainty. Tallow, obtained by heating the suet of cattle and sheep

[2] Much of the material in this section was obtained from references 20 and 21.

under pressure in closed vessels, had long been used to make candles and soap. The basic process for soap making was to boil fat or oil with strong alkali. For hard soap, soda made caustic with lime was used. For soft soap, a caustic potash was used, prepared by treating wood ashes with lime. The glycerol, fatty acid salts, and the excess alkali were all probably incorporated into the final soap. It was not until the 17th century that the fatty acid salts (soap) could be made to separate by adding salt to the mixture.

The expansion of industry (including textiles, glass, and soap) in the latter part of the 18th century put a large strain on natural sources of alkali. The acute shortage in France prompted the French Academy in 1775 to offer a prize for a method to make soda (sodium hydroxide) from salt. Nicolas Leblanc developed a process (patented in 1791) in which salt was treated with sulfuric acid, and the resulting salt-cake (sodium sulfate) was mixed with coal and limestone and roasted. Soda was then extracted with water from the resultant black ash, and the solution was evaporated to dryness in open pans. The Leblanc process was extremely important in that it was the first large scale industrial process and, in conjunction with the work of Chevreul on the saponification of fats in 1809, it allowed the large scale production of soap.

During the 17th and 18th centuries chemists analyzed organic substances primarily by distillation methods. These procedures were derived from the practices of the medieval alchemists and distillers who discovered alcohol and mineral acids, and the medical herbalists who used distillation methods to prepare essences of plants to be used as drugs. The distillation analyses produced variable products because the properties and amounts of the decomposition products varied according to the conditions of the distillation. The products derived from different substances were not very different. The introduction of Fahrenheit's thermometer into the distillation apparatus allowed some degree of control of the process, but it was still not possible to isolate substances whose properties gave to each type of plant material its unique characteristic. In the middle of the 18th century chemists began to use solvents (water, ether, and alcohol) as well as solvent extraction and distillation procedures together, and new substances theretofore unknown were isolated.

As long as chemists lacked methods for determining chemical composition, they could only describe the substances they isolated by their physical and chemical properties. This changed at the end of the 18th century. One of the most important discoveries in the late 18th century was that organic substances are composed mainly of four elements—carbon, hydrogen, oxygen, and nitrogen. This realization allowed chemists not only to classify organic substances but to explain chemical, and even biological, transformations of these substances. Procedures developed by Berthollet and Lavoisier made possible the determination of the elementary composition of organic substances. Analyses of plant substances by Lavoisier showed a correlation between elemental analyses and previous classifications according to physical and chemical properties. He showed that the fats and oils consisted primarily of carbon and hydrogen, whereas sugars and starch contained these elements plus oxygen. He therefore considered that these latter substances were oxides of fats and oils. Lavoisier's analyses of plant substances by oxidation yielded carbonic acid and water. He surmised that the reverse reaction takes place in the living plant, i.e., the carbon of carbonic acid joins with the hydrogen of water to form oils, and the remaining oxygen is released as a gas.

One of the major figures in the development of organic chemistry and the chemistry of natural fats was Michel Chevreul. He started his long career at the Museum of Natural History in Paris in 1803 where he studied chemistry under Nicolas Vauquelin. When he began his study of the natural fats in 1811, organic chemistry was in a very rudimentary state. Neither the saponification process itself nor the nature of the ingredients and products were understood. The first area of organic chemistry to undergo a thorough investigation was animal fats, and as a result of Chevreul's studies the fats were the first class of naturally occurring substances whose chemical character was understood.

In one of Chevreul's initial studies he treated a potassium soap obtained from pig fat with acid, and obtained a crystalline material with acidic properties. This was the first isolation of a fatty acid. Chevreul eventually isolated, studied, and named many fatty acids from butyric to stearic. He established that saponification of animal fats with alkali yielded fatty acids and glycerol, and that saponification was the chemical fixation of water in which the alkali replaced glycerol in combining with fatty acid. Chevreul inferred that fats were comparable to esters. In order to carry out his experiments, he introduced many original techniques, including methods to separate fatty acids on the basis of fractional solubility in various solvents. The fatty acids were purified by repeated crystallization, and purity was determined by constancy of melting point. It was Chevreul who was primarily responsible for the introduction of melting point as a means to assess purity of an organic compound. His studies of the natural fats became a model of analytical research in organic chemistry. In the latter half of the 18th century the major constituent of most gallstones was found to be a white substance that was soluble in alcohol and ether. Chevreul named this material "cholesterine" (Gr. *chole,* bile; *stereos,* solid).

Chevruel's papers were individually published in the *Annales de Chimie.* They were later collected and expanded, and published in 1823 in his *Recherches Chimiques sur les Corps Gras.*

Other chemists in the first half of the 19th century contributed to the chemistry and biochemistry of fats. William Prout was an English physician and chemist. (He is known for his discovery of HCl in gastric juice in 1824). On the basis that milk contains fat, a sugar, and casein, and that related substances are the primary constituents of plants and animals, he concluded in 1827 that nutrients can be divided into three classes: "saccharine", "oleaginous", and "albuminous". He regarded oleaginous substances (fat) as combinations of different amounts of water with "olefiant gas" (ethylene).

Pierre Berthelot, in a sense, extended Chevreul's studies. He also worked with fats, and his doctoral thesis (1854) dealt with the synthesis of fats by combining glycerol with fatty acids. He demonstrated that one equivalent of glycerol combined with three equivalents of fatty acid. Berthelot's studies were significant because by combining glycerol with fatty acids that did not occur naturally, he was the first to synthesize an organic substance that did not exist in nature. Berthelot also showed that cholesterine was an alcohol; this resulted in a name change of the substance to cholesterol. The presence of this material in animal tissues was known in the 1840's, and Vogel in 1843 showed that it was present in atheromatous lesions of human arteries.

Justus Liebig studied under Gay-Lussac in Paris, and perfected and simplified procedures for elementary analysis of organic compounds. One of his most significant innovations was the trapping of CO_2 in KOH without first collecting the gas. From the amount of CO_2 and water formed on complete combustion, he was able to determine accurately the carbon and hydrogen in the original material. Liebig published his *Animal Chemistry* in 1842. He believed that quantitative elementary analysis would reveal the laws of chemical transformation in nature, and thus show how the composition of body substances is maintained by addition and removal of constituent elements of ingested food, respiratory gases, and excretion products. The first edition of his book contained equations that were sharply criticized by Berzelius and Kohlrausch. For example, Liebig sustained his contention that sugar is converted to fat by formulas that showed that removal of 4 equivalents of water and 31 equivalents of oxygen from 3 equivalents of milk sugar produces cholesterine, the fat of bile. Liebig also suggested that the extra carbons from the breakdown of protein (i.e., after excretion of uric acid or urea) are carried to the liver and secreted as choleic acid, the main constituent of bile. After the bile enters the intestine, the choleic acid is reabsorbed into the circulation and then oxidized in the capillaries to CO_2 and water. Although Liebig maintained that his equations were attempts to define questions about metabolic reactions that might serve as the basis of future studies, he exercised greater caution in deriving his theories in later editions of his book. He no longer justified his argument that fat is formed from sugar on the basis of the equation outlined above. The criticisms of Liebig's ideas notwithstanding, Liebig had demonstrated that the formation of various substances in the body could be depicted as chemical processes, and his studies had accustomed physiologists to regard biological phenomena in terms of such processes.

An overview of lipid chemistry in the latter half of the 19th century would not be complete without brief mention of two important scientists, Hoppe-Seyler and Thudichum. Hoppe-Seyler's contribution to fat chemistry was his discovery of the phospholipid lecithin. He also started, in 1877, the first scientific journal devoted entirely to biochemistry. Thudichum excelled in many areas of chemistry and medicine, and his treatise on the chemical constitution of the brain is well known (19). However, because of his controversies with Hoppe-Seyler, he was never in his lifetime given the credit due him for this classic work.[3]

In the Editorial preface to this special issue, Dr. Marsh commented on Thudichum's *A Treatise on the Chemical Constitution of the Brain* in 1884 as being the real beginning of lipid research as we understand it today. Perhaps a fitting close to this 2000 year overview of fats and lipids would be to quote from the preface of Thudichum's book (19).

"Phosphatides are the centre, life, and chemical soul of all bioplasm whatsoever, that of plants as well as animals. Their chemical stability is greatly due to the fact that their fundamental radicle is a mineral acid of strong and manifold dynamicities. Their varied functions are the result of the collusion of strongly contrasting properties. Their physical properties are, viewed from a teleological point of standing, eminently adapted to their functions. Amongst these properties none are more deserving of further inquiry than those which may be described as their power of colloidation. Without this power no brain as an organ would be possible, as indeed the existence of all bioplasm is dependent on the colloid state."

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[3] For comments on the controversies between Hoppe-Seyler (and his colleagues), and Thudichum on the chemical constitution of the brain, readers are referred to *Reflections upon a Classic,* written by David L. Drabkin as an introduction to reference 19.

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