THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 287, No. 42, Issue of October 12, pp. 35439–35441, 2012

Published in U.S.A.

Classics

Essential Fatty Acids: The Work of George and Mildred Burr

A New Deficiency Disease Produced by the Rigid Exclusion of Fat from the Diet (Burr, G. O., and Burr, M. M. (1929) *J. Biol. Chem.* 82, 345–367)

On the Nature and Role of the Fatty Acids Essential in Nutrition (Burr, G. O., and Burr, M. M. (1930) *J. Biol. Chem.* 86, 587–621)

In the early 1900s, dietary fat was viewed simply as a source of calories, interchangeable with carbohydrates, but in 1929 and 1930, a husband-and-wife team published two papers in the *Journal of Biological Chemistry* that turned the notion on its head. Through meticulous analyses of rats fed special diets, George and Mildred Burr discovered that fatty acids were critical to health. If fatty acids were missing in the diet, a deficiency syndrome ensued that often led to death. The Burrs identified linoleic acid as an essential fatty acid and coined the phrase "essential fatty acids."

George O. Burr in 1980. This photograph was provided courtesy of the Eskind Biomedical Library, Vanderbilt University Medical Center.

The work by the Burrs "showed that fats are not there solely as calories to support growth but that they are important for proper physiology," explains Norman Salem, Jr., of DSM Nutritional Products, a company that makes bulk vitamins, lipids, carotenoids, and other nutrition products. The two papers heralded "the beginning of a modern paradigm in nutritional biochemistry."

The field of nutritional fatty acid research has exploded since the work by the Burrs and now affects our daily lives. Food manufacturers add fatty acid supplements, such as the omega-3 fatty acids eicosapentaenoic and docosahexaenoic acids (more popularly known as EPA and DHA), to processed foods, and government agencies work to establish guidelines on which fats should be incorporated into healthy diets.

In a speech he gave in 1980 at the Golden Jubilee International Congress on Essential Fatty Acids and Prostaglandins at the University of Minnesota, George Burr recounted how he stumbled into the research project that changed the perception of fats (1). In 1924, as a freshly minted Ph.D. in biochemistry from the University of Minnesota, 28-year-old Burr joined the staff of Herbert Evans at the University of California, Berkeley. Evans was already famous because he, along with Katherine Scott Bishop, had discovered vitamin E two years earlier. Burr joined the laboratory as a research associate and was tasked with understanding the chemistry of the vitamin.

At the time Burr arrived at the Evans laboratory, armed with a Gila monster he had recently captured on an Arizona scientific expedition and then had stuffed, his colleagues were grappling with a problem. They were trying to produce sterile female rats as controls for an assay with a diet deficient in vitamin E, but for some reason, the rats were not always sterile. It seemed that some lipid component with vitamin E in it kept sneaking into their diet.

To tease out the details, George Burr put a group of rats on a highly purified and simple diet. The diet consisted of sucrose and casein, both of which he and his colleagues repurified after they received them from the manufacturers to make sure there were no trace components that could somehow affect results. They added components such as highly purified salts and vitamins to the sucrose and casein and then fed the concoction to the rats. "In a little while, we had an extreme deficiency in our young animals," Burr said in the 1980 speech. "We had run our first fat deficiency experiment and didn't know it."

The researchers searched the literature to figure out where they had gone wrong. They had added all the known vitamin supplements to the simple diet, but they were still getting a deficiency syndrome. Burr said in his 1980 speech that nutrition experts of the time insisted to him that fats were not necessary for a complete diet.

As he tried to figure out what was going on with the sick rats, Burr accepted an offer to join the new Department of Botany at the University of Minnesota. By this time, he was married to a technician named Mildred (maiden name of Lawson), who was responsible for the Evans laboratory's stock rat colony. So that George Burr could start his new post in 1928, the couple left Berkeley, California, for Minneapolis, Minnesota, in a Model T Ford with two cages of rats. "On the cold fall nights, our pets were smuggled into hotel rooms under long overcoats," George Burr recalled in an 1981 article (2).

While George Burr had the appointment at the university, funding was so tight that Mildred volunteered to help with the work (3). The Burrs felt that if they were to make any headway with this nutritional syndrome they had on their hands, they had to exclude fats more rigorously from the simple diet, and they had to quantify the symptoms of the deficiency as thoroughly as possible. This way, they would be able to measure the relative curative properties of additives they put in the simple diet later on.

In the 1929 JBC paper, the Burrs described the new nutrition deficiency in detail. When fats were eliminated from the diet for several months but the amount of food was not changed, the rats developed scaly skin. Their tails became inflamed and soon ridged with scales. The hind paws reddened and sometimes swelled. The fur on the back filled with dandruff. The animals lost fur around the face and throat, and sores appeared. As they continued on the fat-free diet, the animals began to lose weight and, within three or four months of the weight loss, died. When they were autopsied, the Burrs noted that the animals' kidneys and urinary tracts bore significant signs of damage. The Burrs showed that the added vitamins did not help the animals recover from the syndrome, but that adding small amounts of lard, as little as three drops, was enough to help the animal recover.

At this stage, the Burrs could conclude only that fat starvation over a period of several months caused a disease in rats that eventually led to death. They did not know if the rats died because of the strain of having to internally synthesize fats or because of the missing fats from the diet.

The second paper, which appeared the next year, put the question to rest. The Burrs showed that linoleic acid was an essential fatty acid that was needed in only small amounts to support health. Their work "led them to identify polyunsaturated fatty acids" as essential nutrients, explains William Smith at the University of Michigan in Ann Arbor.

The Burrs established that the fat-deprived rats could not be cured with saturated fatty acids, such as stearic, palmitic, and lauric acids. However, if the rats were given linoleic acid from sources such as olive oil, lard, or linseed oil, they were cured. The Burrs went on to show that complex unsaturated oils like corn and cod liver oils were better at curing the animals than just a single fatty acid or phospholipid. They had to use physical and chemical means of separation to analyze the components of the fats because their work preceded the days of common analytical techniques, such as thin layer and gas chromatography, spectroscopy, and automatic fractionating methods.

Their findings were "born into controversy" wrote Ralph Holman of the Hormel Institute in 1988 (3). In the 1940s, Holman was one of George Burr's graduate students and later a research associate. Holman pointed out that in the same issue of JBC as the second paper, a group led by Lafayette B. Mendel at Yale University had a paper that concluded that fat's nutritional value was solely in fat-soluble vitamins and calories but not fatty acids (4). In his 1981 article, George Burr remembered receiving a letter of condolence for coming to the conclusion that fatty acids were important (2).

Later work (some of it done by Holman) went on to demonstrate that linoleic acid was critical in the human diet (5, 6). As more research gave credence to the Burrs' work, a different mindset took hold that went to the other extreme. Nutritionists believed that linoleic acid was the only essential fatty acid. "The idea that linoleic acid was *the* essential fatty acid persisted for a long time, even into the 1990s," says Salem. He adds that the thinking was so pervasive that linoleic acid was the only fatty acid required to be added to infant formula. It was only in the mid-1990s that the World Health Organization "said infant formula should have a fatty acid distribution more like human milk, which contained other long-chain, polyunsaturated

fatty acids as well," says Salem, citing the omega-3 and omega-6 fatty acids DHA and arachidonic acid as examples.

Salem says that modern nutritional biochemists can learn a lesson from the Burrs' experimental procedures. By keeping the diet very simple and repurifying the proteins and sugars, the Burrs "invented the whole approach of how to exclude fat from the diet. It is a mistake people still make today," he says. Salem explains that researchers get waylaid by the description "fat-free" in a product catalog, not realizing that the product may have traces of fat still in it. The Burrs did not take those risks. They went to great lengths to make sure that all the materials they were using to design the diet were truly devoid of any traces of fat.

The skin symptoms in the Burrs' rats were striking. It is only now that some understanding of how linoleic acid plays a role in maintaining healthy skin is starting to emerge. In a recent JBC publication, recognized as one of the "Best of JBC 2011" papers, Alan R. Brash's group at Vanderbilt University proposed an explanation for the critical role of linoleic acid in building the water barrier in the skin (7). Brash says that the Burrs noted that the fat-deprived rats lost more water through their scaly skin. By using a series of analytical techniques, Brash's group demonstrated that two particular lipoxygenases are responsible for oxidizing linoleic acid esterified in a special ceramide to allow the subsequent covalent bonding of epidermal proteins and ceramides together to produce a functional barrier to water loss.

Mildred Burr died in 1962. George Burr's career later took him to Hawaii and Taiwan, where he worked on photosynthesis in agricultural crops. Burr was the first to discover that sugarcane used C4 carbon fixation. He died in 1990.

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DOI 10.1074/jbc.O112.000005

William Smith at the University of Michigan Medical School (JBC Associate Editor) nominated the papers as Classics, and Rajendrani Mukhopadhyay (ASBMB's Senior Science Writer) wrote the introduction.