ESSENTIAL FATTY ACIDS AND INFANT NUTRITION

Borden Award Address

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ARILD EDSTEN HANSEN was born in Minneapolis during the last year of the last century and grew up in that city. He was educated in the schools of Minneapolis and at the University of Minnesota where he received his degrees: B.S. in 1923, M.B. in 1924, M.D. in 1925 and Ph.D. in 1934. Arild Hansen also spent the years 1929 and 1930 in post-graduate studies at Heidelberg and Vienna. He served the University of Minnesota as an Assistant and an Instructor of Pediatrics until 1934. The year 1934-35 was spent as an Alexander Brown Coxe Fellow at Yale University. Upon returning to Minnesota, Dr. Hansen became Assistant Professor of Pediatrics, in 1937 Associate Professor and in 1942 Professor. In 1944 Dr. Hansen traveled from the extreme north to the extreme south of the United States to become Professor of Pediatrics and Head of the Department at the University of Texas Medical Branch in Galveston. Dr. Hansen is a member of numerous scientific societies. He has a long career in investigation and published many articles on a variety of topics but especially on lipid metabolism.

In a presentation such as this, no doubt, one is allowed the equivalent of a certain degree of "poetic license" in reviewing the work which has led to commendation by the Committee on Awards of the American Academy of Pediatrics. Collaboration is not only an essential feature of present-day investigative endeavors, but also a social reward. As with everyone else, perhaps, who has attempted to pursue "ideas," the writer has found persons who stand out as vital and indispensable in seeking to establish fantasy or fact in relation to concepts conceived. In regard to the subject of the essential fatty acids, it has been my pleasure and privilege to work in the most stimulating manner with the late William R. Brown, Mildred R. Ziegler, George O. Burr, Irvine McQuarrie, William R. Wilson and in recent studies for which this award is being given with Doris J. D. Adam, and especially with Hilda F. Wiese of the University of Texas School of Medicine.

Each of us can recall events from our school years which have harried us long after their direct relationship to the subject has been forgotten. A statement during my premedical days, which for some reason or other stuck as "gum to a shoe," was made by Professor Lee I. Smith of the Department of Organic Chemistry while discussing the subject of fat. After mentioning that the fatty acids found in nature have an even number of carbon atoms, he added, "there are some which have unsaturated linkages, but no one knows the reason for this." I still recall placing a question mark in my notebook to indicate "I wonder why."

EARLY CLINICAL AND CHEMICAL OBSERVATIONS

It was purely a clinical impression some years later, which stimulated my interest in the significance of dietary fat, particularly in regard to the essential nature of certain unsaturated fatty acids in human nutrition. In caring for the infant with eczema, it was the general therapeutic practice to remove fat from the diet. During my hospital-training years, as well as in private practice, I followed this procedure; however, the results were unimpressive. Still, the problem of eczema seemed to offer a challenge, especially after I had visited a...
number of the Children's Hospitals of Europe and noted the uniformity of the problem, i.e., similarity of manifestations and difficulty in management.

It was about this time that Burr and Burr had published their astute observations on the effects of fat-free diets on rats. The idea that lack of dietary fat could produce profound changes in the appearance of the skin, which were cured by the addition of special fats to the diet, was an alluring idea. After some deliberation, this new approach to the problem of eczema was tried. A number of infants suffering with eczematous eruptions were given supplements of fats, such as fresh lard, corn oil or raw linseed oil, which contain unsaturated fatty acids. In none did the eruption become worse; whereas, after several weeks some infants appeared to be definitely improved.

It was these clinical observations which led me to the laboratory to learn something about lipid analysis in order to study blood fats. It was found that the iodine numbers of the fatty acids of the serum of infants with eczema were lower than those of infants free from such skin eruption. In our initial studies it was found that with no essential difference in the concentration of the total fatty acids of the serum, the iodine number of the fatty acids was 84 on the average in the infants with eczema compared with 111 in control infants (Table I). Following the administration of dietary fats which contained unsaturated fatty acids, the iodine values of the serum fatty acids were found to be in the same range as for the control subjects. The changes in iodine number of the fatty acids frequently coincided with clinical improvement. After discussing these observations with Dr. McQuarrie he suggested that I see Dr. Burr who was a member of the Department of Botany in the same institution. From him it was learned that no studies of the serum fatty acids in rats had been made, but he agreed that such a project was worthy of pursuit.

Arrangements were made to analyze the serum lipids of fat-deficient and control rats. The results showed that the difference in iodine numbers of the serum fatty acids between animals suffering from fat deficiency and healthy control animals was of the same order of magnitude as was observed between eczematous and control infants. As indicated in Table II, subsequently this also was found to hold for dogs. These preliminary observations indicated that a thorough study of blood lipids in relation to dietary fat might be helpful in evaluating the role of fat in the maintenance of healthy skin. However, to conduct such a study two features were apparent: Firstly, a method for the determination of specific fatty acids in blood serum would assist materially in carrying out such a project; secondly, actual experience with low-fat diets would be necessary to establish an essential role of fatty acids in human nutrition.
DEVELOPMENT OF METHODS FOR LIPID ANALYSIS AND THEIR APPLICATION

The first step in the development of methods was a semimicrogravimetric procedure for the direct determination of fat by Wilson and Hansen, \(^8\) wherein it was possible to separate the fatty acids from the unsaponifiable fraction. Further fractionation allowed one to determine the amount and average degree of unsaturation of the fatty acids present as phospholipids. \(^9\) Subsequently, by means of alkaline conjugation of unsaturated fatty acids and spectrographic analysis by the method of Wiese and Hansen, \(^10\) it was possible to measure the amount of the 2-, 3- and 4-double-bond fatty acids in blood serum and body tissues.

Next, in order to establish correlations between dietary fat and clinical appearance of the skin, as well as between dietary fat and concentration of specific fatty acids in the serum, an extensive series of experiments were carried out with young puppies. \(^11-14\) Incidentally, our first efforts at feeding a diet extremely low in fat to dogs resulted in vitamin E deficiency, which was evidenced by the development of paralysis of the hind extremities. Recovery occurred with the addition of alpha-tocopherol to the diet, but not by the addition of fat.

To date, well over 100 dogs have been studied, some of which have been under observation for as long as 6 years. These studies established the following facts:

1. Signs of fat deficiency readily develop in young puppies. These are characterized by dryness of the skin and loss of hair, desquamation, erythema and pigmentation of the skin, running of the ears, oozing of the paws and a tremulous, nervous behavior. Some of these signs are not unlike those observed in some infants who have been on diets very low in fat. The rate at which the symptoms of deficiency in dogs disappear is directly related to the quantity of linoleic acid in the diet. Examples of control and fat-deficient dogs are shown in Figure 1.

![Fig. 1. Young dogs of same age since weaning (a, left) fed on diet in which fat (fresh lard) comprised 29% of the calories and (b, right) same diet except sucrose substituted for fat (total fat 1% of total caloric intake).](image)

Adult dogs did not show the severe signs of deficiency which were observed in young animals. In spite of a caloric intake per unit body weight equal to that of control animals, marked emaciation ultimately develops in young animals which do not receive fat in the diet.

2. Histologic examination reveals marked alterations in the structure of the skin of fat-deficient animals. There is parakeratosis with peeling of the outer layers and pres...
ence of nucleated cells in the stratum corneum, an increase in the cell layers of the epidermis and hair follicles, plugging of the hair follicles, increased activity in the sebaceous glands and later signs of atrophy, evidence of activity of sudoriparous glands, infiltration of the dermis and uneven collagen fibers. Examples of the skin changes in control and fat-deficient animals are shown in Figure 2. The rate at which the abnormal histologic structures disappear is related to the linoleic acid content of the dietary fat.

3. Although the iodine number of the serum fatty acids of dogs decreases with a low-fat diet as indicated in Table II, greater significance is assigned to the direct correlation between dienoic (linoleic) acid content of the serum and the linoleic acid content of the diet. The concentration of tetraenoic (arachidonic) acid in the serum changes in the same direction as that of dienoic acid, whereas the change for trienoic acid is in the opposite direction (Table III). The increase in trienoic acid in fat-deficient animals is a subject of considerable interest to a number of workers in this field.

It was concluded from the studies with dogs that: Young subjects appear to be much more sensitive to a lack of fat in the diet than adults; dermal structures are affected particularly; metabolic processes concerned with utilization of calories are altered; and measurement of the di-, tri- and tetraenoic acids of the blood serum (2-, 3- and 4-double-bond fatty acids) might well give one an index for determining the requirement for unsaturated fatty acids in the diet of infants.

ATTEMPT TO ESTABLISH THE INFANT'S REQUIREMENT FOR UNSATURATED FATTY ACIDS

Clinical Observations on Human Subjects Maintained on Diets Low in Fat

During the first short-term studies of infants given diets low in fat, it was observed that impetiginous skin eruptions were difficult to heal. One infant with chylous

| Table III | UNSATURATED FATTY ACIDS IN SERUM OF DOGS[^10] |
|---|---|---|---|
| Diet | Total F.A. (mg/100 ml) | Diienoic | Trienoic | Tetraenoic |
| Low-fat Fat (lard) 30% of calories | 367 | 5.2 | 15.9 | 3.3 |
| | 479 | 22.7 | 1.2 | 11.1 |
ascites,\textsuperscript{15} who for almost 2 years was given a diet very low in fat, showed: (1) Normal increase in height (not possible to evaluate weight curve); (2) food consumption greater than expected; (3) evidences of disturbed skin function as indicated from development of a chronic dermatitis following prickly heat, periodic eczematous lesions and resistance to treatment of impetigo.

An adult subject\textsuperscript{16} for a 6-month period was maintained on a diet low in fat (composed of skimmed milk, cane sugar, potato starch, baking powder, sodium chloride, orange juice, ferric chloride, Viosterol\textsuperscript{17}, and carotene, with liquid petrolatum incorporated as a shortening in the attempt to make something equivalent to biscuits); the total fat intake was not more than 2 gm per day. Rats maintained on the same diet developed typical signs of fat deficiency. The adult subject maintained a state of well being during the 6-month period. At the beginning of the study the blood pressure bordered on the hypertensive level, but while on the low-fat diet was within the normal range. During this time he did not suffer headaches to which he had been subject periodically. He lost 14 pounds in weight in spite of a caloric intake and degree of physical activity similar to that to which he was accustomed both before and after the special-diet period. Determinations of the respiratory quotient indicated that the human subject reacted metabolically similar to the rat.

These observations of an infant with chylous ascites and of an adult subject are presented in some detail because of subsequent findings in two large groups of infants. In a study of 20 infants under 1 year of age, fed diets containing variable amounts of fat and linoleic acid, it was observed on several occasions that use of a low-fat diet was associated with changes in the skin. In another more extensive study which is now underway, it has been demonstrated that linoleic acid plays a definite role in the maintenance of healthy skin in young babies.

\textbf{Chemical Observations on Serum Lipids}

With a diet low in fat, in human subjects, the iodine number of the serum fatty acids decreases. More significant, however, seems to be the observation\textsuperscript{17} that the 2- and 4-double-bond fatty acids decrease while the 3-double-bond fatty acids increase. Although the values for the unsaturated fatty acids in human subjects and dogs are different, the change is in the same direction as has been noted for dogs.\textsuperscript{18} This phase of our studies will be discussed in greater detail in subsequent reports.

\textbf{Caloric Consumption in Relation to Linoleic Acid Intake}

Although studies relating the caloric intake to linoleic acid in the diet have been completed, only preliminary reports\textsuperscript{19} have been presented. We are desirous of acknowledging the valuable assistance in these studies provided by a contract from the United States Department of Agriculture, Human Nutrition Research Division. The study was undertaken primarily to ascertain whether or not one could determine the infant’s requirement for linoleic acid by using the concentrations of di-, tri- and tetraenoic acids in the serum as an index of adequacy of intake. Milk mixtures were fed which varied in contents of fat as well as linoleic acid. Close relationships were found between the concentration of the unsaturated fatty acids in the serum and the linoleic acid intake (Table IV).

In addition, careful clinical observations and ordinary laboratory studies were made and accurate records of the food intake were kept. When the caloric intakes and the body weights were fitted to straight lines, it was found that the caloric intake varied with the linoleic acid content of the milk mixture. The data from a male infant who was 2 weeks of age at the beginning of the study are presented graphically in Figure 3. One may note no essential change in the slope of the weight curve whether the infant received the skimmed-milk preparation (contained 1% of the calories as fat,
TABLE IV
LIPID IN SERUM FROM INFANTS CONSUMING MILK OF VARIABLE CONTENT OF
FAT AND LINOLEIC ACID

<table>
<thead>
<tr>
<th>Diet</th>
<th>No. of Infants</th>
<th>Total F.A. (mg/100 ml)</th>
<th>Dienoic (per cent of TFA)</th>
<th>Trienoic (per cent of TFA)</th>
<th>Tetraenoic (per cent of TFA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-fat</td>
<td>3</td>
<td>292</td>
<td>5.2</td>
<td>4.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Evaporated milk</td>
<td>4</td>
<td>282</td>
<td>10.4</td>
<td>3.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Breast milk</td>
<td>4</td>
<td>287</td>
<td>23.1</td>
<td>0.4</td>
<td>10.6</td>
</tr>
</tbody>
</table>

0.04% of the calories as linoleic acid) or the evaporated-milk mixture (contained 40% of the calories as fat, 1% of the calories as linoleic acid). Both preparations contained 20 calories per ounce.

At the beginning of the study this infant was consuming food at the rate of about 110 cal/kg/day. After 4 weeks this had increased to about 160 cal/kg/day. As soon as fat was added to the diet, in an evaporated-milk formula, a definite decrease in the calories consumed per unit body weight occurred, so that after 4 weeks he was consuming food at the rate of about 100 cal/kg/day. The average gains in weight were 25 and 27 gm/day on the skimmed-milk and evaporated-milk mixtures, respectively.

In the final report of the study, data will be presented which indicate that a similar decrease in calories consumed per kilogram per day occurred when the skimmed-milk mixture was supplemented with small

![Diagram](image)

**Fig. 3.** Data from an infant who was fed a skimmed-milk mixture from 2 to 6 weeks of age and an evaporated-milk mixture from 6 to 10 weeks of age.
amounts of linoleic acid. It appears that linoleic acid plays a significant metabolic role in infant nutrition. This tentative conclusion is based on incomplete evaluation of data obtained from study of 20 different infants.20

Finally, it may be of interest to note that the presentation of the Borden Award on behalf of the American Academy of Pediatrics for 1957 is being made to one who comes from the same town (Galveston) where Gail Borden carried on his work which led to his epoch-making discovery. The one hundredth anniversary of his company is now being celebrated. Just last week I visited his homesite, read some of his original communications in our city (Rosenberg) library, and was again impressed with the extraordinary versatility and accomplishments of this unusual man. He lived in Galveston from 1837-1851 and returned there just a century ago to join his family before going on to seek further financial assistance to put his discovery of a process for evaporating milk to use. It was in Galveston in 1840 that Gail Borden, Jr. made his basic observations regarding the evaporation of milk under vacuum to produce a product which would stay clean for long periods. It is noteworthy that he did not undertake his investigative efforts strenuously until he was approaching 50 years of age. Among his accomplishments we find that as a surveyor he compiled the first topographical map of Texas and laid out the City of Galveston. He published the first newspaper in Texas (Telegraph and Texas Register) in which was first printed the Declaration of Independence of Texas (1835) as well as its Constitution which he helped to write. He was the first collector of customs and helped to organize the First Baptist Church in Galveston (his mother was a great, great granddaughter of Roger Williams). He was a close friend, counsellor and collaborator of the great leaders and patriots of Texas, Stephen F. Austin and Sam Houston. After diligent endeavors he invented a meat biscuit which received acclaim, but failed to impress the food buyers for the army, yet orders from England indicated that his product was sent to Florence Nightingale to help her in her plight during the Crimean War. Mr. Borden went to England where he received The Great Counsel Medal at the London International Exposition. Upon returning to Galveston in 1851 the cows on board ship became ill, and he observed that the infants on ship also became ill and some died. Apparently, it was this experience which spurred him on to work upon his idea of milk processing to produce a clean milk. He believed in cleanness of milk long before the concept of microbes had been introduced. What he learned in pursuing the idea of making a desiccated meatball or meat biscuit and the accidental discovery of a method for keeping milk clean and safe has been the turning point in the lives of many men.

Let this be an inspiration to us all, old and young, in medicine and science: Casual observations, if carefully made, often prove to be more than incidental in importance!

REFERENCES

8. Wilson, W. R., and Hansen, A. E.: Study of the serum lipids by a microgravimet-


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