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Nutritional Research: What Benefits Besides Nutrition?

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The honor of being elected President of the American Pediatric Society affords me the opportunity to express some thoughts gleaned while studying nutrition in infants. More than nutritional lessons can be learned from observations of infant feeding practices as they have developed over the past 3–4 decades. In reviewing some of these one becomes impressed more than ever with recognition that today's dogma may be tomorrow's anathema.

Consider the new dietary guidelines, which logically should apply to all ages. While allegedly based on the desired goal of a healthier, happier society some of the recommendations, like those referable to reducing alcohol and total fat and consuming a variety of foods, excite little argument. But when one approaches the recommendation concerning dietary cholesterol in order to avoid arteriosclerosis, one is confronted with questions about the rationale which indeed would exclude breast milk for the infant. It is true that the dietary guidelines exclude recommendations and are not designed for the infant, but somewhat more concrete evidence concerning dietary cholesterol seems desirable before making so broad a recommendation for masses of people.

Developments in nutrition for children over the past 50 yr serve to encourage approaches to research not only in nutrition but also in other areas of investigation. The acceptance of breast feeding as a standard is gratifying. Fifty years ago the goals of infant nutrition were clear and concise. Infants would be nursed for a year. Vitamin C could prevent or cure scurvy. Vitamin D could prevent or cure rickets. With the desire for more choices, infant formulas were made somewhat like breast milk and would free the nursing mother to allegedly better enjoy more spare time either without harming or actually benefiting the infant. One minor problem was the relatively unimportant one of how to feed prematurely born infants so that they would grow faster. More rapid growth would allow premature infants to be discharged from the hospital sooner. Everyone knew that most premies who died did so in the first 3 days when nutrition was unimportant as a cause of death, or they died after 3 days, usually of infection. The hospital was (and is) a source of infection, and the sooner at home, the better.

It was recognized at that time that low birth weight infants absorbed saturated fats poorly. Thus, popular formulas for premature infants contained small amounts of fat, and caloric density was made up with protein and carbohydrate (1) (Table 1). As a result many infants developed hyperammonemia and diarrhea. In addition, hyperelectrolytemia and water retention were common complications (2). When it was recognized that premature infants were able to utilize human milk fats, low birth weight infants were tried on simulated human milk formulas with modification of the type of fats. Cow's milk fat, largely saturated, was found to be poorly absorbed by low birth weight infants. Substituting at least part of the butter fat with the unsaturated vegetable fats led to a marked increase in absorbability as well as satisfactory growth and a decrease in incidence of diarrhea (3).

Cow's milk whey was, for unknown reasons, believed to be better for these infants than casein (4). The significance of whey as compared with casein still remains controversial in infant nutrition studies (5). Cow's milk whey protein contains more cysteine than does casein and since the prematurely born infant has limited ability to metabolize methionine (6), and because the digestibility of cow's milk whey is superior to that of casein, there may be some real advantages to feeding premature infants whey protein (7). Human whey may be superior to cow whey. The advantages of human milk whey have been proven for its immunological properties and unique protein composition.

There was an attempt to make low birth weight infants grow faster by feeding a formula with a caloric density of 150 cal/100 ml, so-called concentrated infant formula (8). Since these formulas were meant to be diluted before feeding and since they were not otherwise modified, growth rates were markedly increased. However, many complications occurred including hyperosmolality, hypocalcemic tetany, and diarrhea. From these early trials, the present 81 and 90 kcal/dl formulas have evolved for premature infants with appropriate modifications in electrolyte and protein composition.

The use of polyunsaturated fats obtained from vegetable oils in infant formulas led to studies of the essentiality of some fats, as well as their effects on calcium absorption and prostaglandin formation (9). Because these fats were so well absorbed, some formulas were made with large amounts of polyunsaturates, sometimes with resultant vitamin E deficiency (10).

A variety of additional modifications of infant formulas ensued using breast milk as a model. Taurine was added, electrolytes were lowered, fat contents were modified to more closely simulate breast milk, protein was raised and lowered, carbohydrate was limited to lactose and then modified with glucose formulations, and still we do not know what is best for low birth weight infants. Experiments with adding cholesterol or further lowering protein, as in breast milk, are proceeding. We now can move the infant out of the hospital faster, but we do not know how to do it better.

The case of lactose is a good example of the interaction of various nutrients. Lactose in association with a relatively low

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Table 1. *Changes in infant feeding practices*

Low fat, high protein, high carbohydrate
Vegetable fat
Whey
Concentrate
Vitamin E
Taurine
Carbohydrate

protein concentration in the formula was shown to produce an acid pH of the intestinal tract and to favor the production of a gram-positive flora—presumed to be advantageous in limiting gram-negative sepsis (11). In addition lactose improved absorption of calcium and decreased the prevalence of neonatal tetany. However, in the prematurely born infant, lactase is not as well handled by the immature intestine, and too much lactose may be associated with malabsorption. Therefore, other sugars have been added—with the expected adverse effects of a changing flora.

The nutritional problems of the prematurely born infant have been progressively defined and include rickets, tetany, infections, necrotizing enterocolitis, salt depletion, salt retention, protein concentration, and others. More subtle problems with the full-term infant now are beginning to surface. Many believe that early nutrition may condition arteriosclerosis, stroke, and hypertension and have recommended decreasing cholesterol, fat, and salt contents and increasing polyunsaturated fat levels in the infant diet. These changes seem logical, but the evidence for benefit except for total fat in the diet, is sparse. Indeed, some of these recommendations may be risky. For example, increasing polyunsaturated fats above a certain level is associated with decreasing plasma levels of high-density lipoprotein cholesterol which in turn may be related to increased vascular risks (12).

There are exciting recent studies of specific and nonspecific antiinfectious substances which may be effective when fed. Some of these have been found in human milk and, as these substances are identified, they may be found useful in other circumstances to improve health of infants and children.

This abbreviated saga of infant feeding practices over the past 50 yr serves to emphasize several lessons (Table 2).

1) The prime lesson to be learned is humility. As we gain new knowledge we develop new questions. Moreover, whenever we attempt to alter natural phenomena, we may expose our patients to considerable risk.

It has been said that God made a compromise in developing breast milk to optimize its value to the infant without unduly harming the mother. This may be true, but before changing human milk we should insist on solid supportive data before we can assume that a superior product is developed.

There are personal references to humility from my own career. First, from my teachers. I have been extremely fortunate choosing my wife, Elaine, my children and my parents; all have taught me much and provided exceptional support. Then my mentors: again, fate smiled on me by providing Charles A. Janeway, John Mitchell, Paul Gyorgy, Bill Wallace, and Sidney Gellis, as well as outstanding chief residents: Fred Robbins, Jim McKay, and C. D. Cook. My colleagues of the past: Robert Kaye, Sidney Friedman, Martin Forbes, and Fritz Zilliken tried to help. Probably most important have been my colleagues-students-teachers including, in more or less chronological order, Enid Gilbert, William Mellman (what a loss when one's student dies before the teacher), Frank Oski (a constant stimulant and critic), Grant Morrow (who did all my work), Michael Miller, David Cornfeld, Lester and David Baker, Thomas Tedesco, Michael Kaback, Stephen Ladisch, Donald Cornely, Allen Root, John Curran, John Malone, Jim Sherman, Jim Hallock, Walter Tunnessen, Leighton Young, and Aree Valyasevi. It is a joy to learn from one's students. This was recognized in the Talmud many years ago. "Much I have learned from my teachers, even more from my classmates, but most of all, from my students." Finally, there were many who helped without fitting any special category. This group includes Maria Delivoria, Susan Carlson, Gerold Schiebler, Bill Cleveland, and others too numerous to name.

Table 2. *Lessons from nutrition*

1. Humility
2. Resistance to change
3. Logic
4. Interrelationships
5. Holistic
6. Animals
7. Mechanisms
8. Expectation
9. Technology
10. Motivation

2) In nutritional research perhaps more than in other fields, resistance to change halts progress. On the other hand, some changes are grasped avidly but without sufficient trial. We need only look at the ready acceptance of the numerous diet and weight reduction books published annually proposing new approaches with minimal if any supporting evidence; or the recent popularity of the ω-3 fatty acids to wonder what long-term results will occur if we adopt major dietary alterations.

3) Arm chair logic is challenging and stimulating but without controlled experiments such logic often leads one astray. From history, one need cite only bleeding for fevers or high colonic enemas for infections. For the present, one might question the possible overuse of total parenteral nutrition which decreases the effort and time required for oral alimentation in difficult-to-feed situations. Which other present practices will be considered absurd by the next generation?

4) In nutritional research as in other fields the interdependence of variables, and in this case nutrients, needs to be remembered. As an example, in the desire to lower sodium in the infant diet, one manufacturer simultaneously lowered chloride with the subsequent development of severe alkalosis in a number of infants. Similar episodes have occurred with alterations of individual minerals and vitamins as well as macronutrients including protein, carbohydrate, and fat.

5) The holistic approach to medicinal research is unlikely to give definitive information. This is not to denigrate the value of holistic medicine. One of the functions of medicine is to alleviate pain and suffering and this requires consideration of the entire patient. However, results so obtained are not research unless prospective protocols are used. In the past when the only expectation of medicine was the relief of pain and suffering, the discovery of more potent analgesics and the laying on the hands sufficed for success of the physician. While the importance of attitude of the physician and patient cannot be overlooked in alleviating suffering, confusion of cause and effect such as occurs with administration of megadoses of vitamin C, and mental attitude in preventing colds or arthritis, only deters from finding lasting or specific treatments.

6) Human research is difficult and complex. The comparative ease of determining nutritional deficiencies or needs in animals or tissue cultures is a delight compared with the multiple variations encountered in humans. But for understanding human requirements, observations in humans are required.

7) Delineation of cause and effect requires discovery of mechanisms. Presuming vitamin deficiencies without clarifying concomitant abnormalities in biochemical-immunological pathways is uncertain. Mineral requirements must be based on demonstrable need and, in suspected deficiency, clear evidence of improvement following supplementation must be documented.

8) Nutrition has been oversold to a gullible public. For a

narcissistic society seeking the fountain of youth in a pill, it seems unreasonable to alter an entire lifestyle in order to truly improve health. Perhaps a pill which bypasses determined effort will be available one day. For the present, pediatricians can attempt to ensure a healthy childhood, and one of the factors is better nutrition. For this, more studies and more attention to infant nutrition and less pragmatic salesmanship are necessary.

9) Nutritional research is entering a new era, particularly regarding children. We have progressed from gross observations of growth and general health—to elimination of deficiencies and avoidance of toxicities—to determination of body composition and determination of utilization of foods by changing body composition—to specific immune functions of foods, the determination of receptors, and the application of genetic techniques for determining specific pathways of utilization. We are approaching the era of determining not only biochemical variability in humans, but also individual requirements for optimal performance.

10) Finally, research is fun for its own sake, but occasionally one gets extra pleasure from seeing important applications and benefits. While it is not delusional to think that investigations may improve mankind, it is the challenge and stimulation of the process that provides most gratification. The tools of research we need are faith, hope, and clarity.

H. L. Mencken stated the process well, "For every complex problem there is a solution that is simple, direct and wrong."

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