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A cholesterol deficiency syndrome in humans.

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Editorial

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Except in crustaceans and insects, cholesterol is not an essential nutrient. Newborn human infants do very well when fed the usual cholesterol-free formulas. In the current preoccupation about "too much" cholesterol, it is important to recognize that every cell of the body requires cholesterol for membrane structure and, in the case of certain endocrine glands, for steroid hormone synthesis. Cholesterol is supplied to most cells by local synthesis and from the plasma through the LDL receptor. However, brain cells, because of the blood-brain barrier, are unique in obtaining their cholesterol by synthesis within the brain (1, 2). Since the brain has the highest concentration of cholesterol of any organ in the body, this means that brain growth and development might well be affected by a deficiency of cholesterol or by aberrations in cholesterol synthesis.

In 1964, Smith, Lemli, and Opitz described a new syndrome characterized in part by microcephaly, severe mental retardation, and hypertonicity (3). The microcephaly indicated impaired brain growth for reasons not appreciated until recently. The biochemical basis for the Smith-Lemli-Opitz syndrome was found to be a block in the synthesis of cholesterol because of a deficiency of the enzyme 7-dehydrocholesterol-Δ-7-reductase, which is required to convert 7-dehydrocholesterol to cholesterol (4). Thus, these patients have low plasma cholesterol levels and, in addition, appreciable levels of 7-dehydrocholesterol not found normally in plasma. It is presumed that brain development is retarded because cholesterol availability is limited for neural growth and perhaps also because 7-dehydrocholesterol is a poor substitute in membrane formation or may even be toxic.

In this issue of *The Journal,* Xu and colleagues (5) have carried their discovery of the enzyme deficiency in the Smith-Lemli-Opitz syndrome to a rat model in which a drug (BM 15.766) was used to inhibit the same enzyme, 7-dehydrocholesterol-Δ^7-reductase. The biochemical abnormalities were reproduced as in the Smith-Lemli-Opitz syndrome: very low plasma cholesterol levels and high levels of 7-dehydrocholesterol. These findings were accentuated by administering cholestyramine which stimulated the pathway for cholesterol biosynthesis. When a high cholesterol diet was fed, the synthetic pathway was depressed through feedback inhibition. Plasma cholesterol levels then increased and levels of 7-dehydrocholesterol decreased. Since rats given BM 15.766 develop the biochemical features of the Smith-Lemli-Opitz syndrome, the patients with this entity might profit also from a high cholesterol diet.

In these patients, perhaps cholesterol is an essential nutrient. Dietary cholesterol would supply cholesterol to the tissues and also reduce the levels of 7-dehydrocholesterol which may have toxicity in itself. Of course, this absorbed dietary cholesterol would not supply cholesterol to the brain because of the blood-brain barrier and the brain is the site of much of the pathology in the Smith-Lemli-Opitz syndrome.

These studies also have two other implications. One is to emphasize the importance of the 7-dehydrocholesterol pathway for cholesterol biosynthesis. With enzyme 7-dehydrocholesterol-Δ^7-reductase, cholesterol biosynthesis may occur without the additional step of going through desmosterol as biochemistry texts have historically indicated. There was no accumulation of desmosterol, thus indicating that its formation, likewise, requires the 7-dehydrocholesterol-Δ-7-reductase as well.

Secondly, there are great hazards in pharmaceutical agents which block cholesterol biosynthesis in its later phases. There is the action of BM 15.766 in the rat, but triparanol is the classic example of a drug which prevented the conversion of desmosterol to cholesterol (6). Given to humans, desmosterol accumulated and cataracts, among other unfortunate side effects, developed. Perhaps even more crucial is the information that interference with cholesterol biosynthesis during the growth of the brain may be especially devastating.

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