Faby's disease is an inherited metabolic disorder in which a lipid called ceramidetrihexoside accumulates throughout the body. The condition was shown to be due to a deficiency of an enzyme that catalyzes the hydrolytic cleavage of the terminal molecule of galactose of ceramidetrihexoside. [The SCIENCE citation index indicates that this paper has been cited in over 290 publications since 1967.]

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"Faby's disease is transmitted as an X-chromosome-linked recessive disorder. Hemizygous males frequently have a reddish-purple maculopapular rash on their skin. They experience acroparesthesias in the hands and feet that get worse with exercise and hot weather. The clinical picture is further characterized by corneal opacities, tortuosity of retinal vessels, generalized atherosclerosis, progressive proteinuria, myocardial infarction and stroke, and eventual renal shutdown. Heterozygotes usually have much milder manifestations although severe signs may be apparent in occasional individuals."

"Original descriptions of this condition were published by dermatologists W. Anderson and J. Faby in 1898. Eventually, it became apparent that there was a generalization of accumulation of lipid in the tissue of these patients. In 1963, Charles C. Sweeley and Bernard Klionsky reported that ceramidetrihexoside [galactosylgalactosylglucosylceramide, CTH] was the major accumulating material in Faby's disease. Much of this lipid is derived from glycolipids in the stroma of senescent erythrocytes."

"In 1965 and 1966, David Shapiro, Julian N. Kanfer, and I synthesized several sphingolipids labeled with 14C with which the metabolic defects in Gaucher's disease and Niemann-Pick disease were established. Based on these findings, I anticipated that Faby's disease was caused by a deficiency of an enzyme that cleaves the terminal molecule of galactose from CTH. However, in 1966, it was not possible to synthesize CTH chemically with a radioactive tracer in the critical terminal molecule of galactose. Andrew L. Gal joined my group and succeeded in labeling ceramidetrihexoside throughout the molecule by exposing it to radioactive hydrogen gas in a sealed vessel (the Wilzbach procedure). Since the terminal galactose contained radioactive 3H, we were able to trace the fate of this moiety. We discovered that mammalian tissues contain an enzyme that catalyzes the hydrolytic cleavage of this galactose and that intestinal mucosa had the highest activity in this regard. Optimal conditions for measuring the activity of this enzyme were determined and lactosylceramide was identified as the product of the reaction. When this information became available, Andrew L. Warshaw and Leonard Laster obtained biopsy specimens of human small intestinal mucosa from 12 controls, from men with Faby's disease, and from the mother of one of the patients. Ceramidetrihexosidase activity was readily demonstrated in the specimens from the controls, whereas no activity was detected in the biopsies from the men with Faby's disease. The activity of the enzyme in the sample from the female carrier was 25 percent of the mean of the controls, a value considerably less than might have been expected for a heterozygote, but compatible with the Lyon hypothesis for X-chromosome inactivation. Furthermore, this level of enzyme activity was consistent with her clinical presentation."

"I believe the paper is frequently cited because Faby's disease is one of the more common sphingolipid storage disorders. Numerous investigations on the pathogenesis of the clinical manifestations in this condition and approaches to the control and therapy of this disorder have been reported. A review of historical aspects and summary of recent studies on Faby's disease is available."