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This Week's Citation Classic

Menkes J H, Hurst P L & Craig J M. A new syndrome: progressive familial infantile cerebral dysfunction associated with an unusual urinary substance. *Pediatrics* **14:**462-6,1954.

The paper describes the clinical course of what the authors later termed 'Maple Syrup Disease,' a syndrome involving a rapidly progressive cerebral dysfunction commencing during the first week of life, and marked by the excretion of urine having a characteristic 'maple syrup' odor. [The *SCI*® indicates that this paper has been cited over 140 times since 1961.]

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"In 1952, I had just begun my internship at Boston Children's Hospital. Peter Hurst was junior resident, and John Craig was the pathologist. The only disorder of amino acid metabolism recognized at that time was phenylketonuria, and although the methodology for paper chromatography had been described some 18 years before, it was used at only one laboratory at the Children's Hospital, that of the late David Hsia.

"The patient was brought in to our medical center because two of three earlier born siblings had succumbed to a disease that was thought to be an atypical form of kernicterus. William Pfeffer had been selected as attending physician, since he had been interested in erythroblastosis.

"In obtaining the infant's history I was told that the mother had noted that the infants who died had an unusual odor, while the girl who was well did not.

"Our baby did indeed develop an unusual odor and shortly thereafter began to have neurologic symptoms. We began to collect urine, and wondered what the odor was. I am sure I must have asked nearly everyone in the hospital, but could get no better reply other than that it smelled like maple syrup. After all, we were in New England.

"One rainy Saturday afternoon Hurst and I went to see Louis Fieser, then Professor of Organic Chemistry at Harvard, and author of the textbook from which I had studied the subject. He was not of much more help, but allowed us to roam through his stock room. Urine bottles in hand, we began to sniff our way through the chemicals. I started at the A's, Peter Hurst at the Z's. Not too much later I had what I then thought was the answer: 'Acid Malic'.

"We were dealing with a disorder of the Krebs Cycle, and an enzyme deficiency which, in analogy to phenylketonuria, caused malic acid to accumulate, and was responsible for the neurologic symptoms.

"Titration of the urine did indeed indicate the presence of an organic acid, but at that point I could go no further. A sample was sent to David Hsia for amino acid chromatography, but not having established norms for newborns, he was unable to help us.

"The infant died, and we used up the last bit of urine for a variety of tests, none of which brought us any closer to the answer. A few months later I did learn from an industrial firm that artifical maple syrup contained a cyclic ketone, and in 1957, when I was given urine from another patient with this disease, I was able to use this information to demonstrate the presence of the branched-chain keto acids[1] and to identify the 'Maple Syrup' odor.[2] By then I was a trainee in Pediatric Neurology and had a research budget —$35.

"I view the importance of this paper as lying not in that it was the first description of a rare disease, but rather in that it emphasizes that the combination of clinical skills (in this instance, obtaining a thorough history) and a good basic science background (in this instance, chemistry) are important ingredients for advancing medical knowledge."

REFERENCES

1. **Menkes J H.** Maple syrup disease, investigations into the metabolic defect. *Neurology* **9:**826-35, 1959.
2. **Menkes J H.** Maple syrup disease, isolation and identification of organic acids in the urine. *Pediatrics* **23:**348-53, 1959.