EDITORIALS

Melamine, Powdered Milk, and Nephrolithiasis In Chinese Infants

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Melamine, a synthetic nitrogenous product found in many industrial goods and even in fertilizer destined for use in growing crops for human consumption, was recently found to have been added to foods in China — including many different powdered infant formulas[1] — to increase their measured, but not biologically available, protein content. Melamine is largely not degraded in humans, although several other compounds (ammeline, ammelide, and cyanuric acid) may become cocontaminants during the manufacturing process, and the main route of excretion after absorption from the gastrointestinal tract appears to be through the urine.[2] The findings of acute kidney failure and symptomatic and asymptomatic kidney stones in infants and children previously exposed to melamine through the consumption of tainted powdered infant formulas have caused great concern. In this issue of the *Journal*, an original article by Guan et al. from Beijing[3] and letters to the editor from Ho et al. from Hong Kong[4] and Wang et al. from Taipei[5] provide readers with substantial information about the relation between exposure to melamine-containing powdered infant formula and nephrolithiasis in infants and children.

Observational data reported by these authors reveal an association between the prevalence of kidney stones as determined on ultrasonography of the kidney at one point in time and a history of melamine exposure based on the amounts in infant formulas as reported by the Chinese authorities. Guan et al. studied 589 children living in or near Beijing whose parents responded to the offer of a free screening; Wang et al. and Ho et al. studied 651 children residing in Taiwan and 2140 residing in Hong Kong, respectively, who underwent testing including ultrasonography of the kidneys.

However, discrepancies in the numbers of exposed children in whom stones developed (and in the categories of exposure to melamine) are found when comparing the three reports. Kidney stones were seen in nearly 10% of the children studied in Beijing who received formula with a high melamine content (>500 ppm) or a moderate melamine content (<150 ppm), and slightly more than 20% of children residing in Taiwan and fed formula with a melamine content exceeding 2.5 ppm had stones. In contrast, only one child residing in Hong Kong and presumably exposed to melamine had a definite kidney stone. How can we best interpret such data to assess the risks for other infants and children who were fed these melamine-contaminated formulas?

One way is to examine the number of people in whom stones would form in the absence of melamine exposure. The estimated number of adults in the United States between the ages of 20 and 74 years in whom stones developed was 5.2% from 1988 through 1994, an increase over the 3.8% from 1976 through 1980.[6] There are no published incidences or prevalences for nephrolithiasis in children, but anecdotal discussions among experts suggest that such rates are currently increasing over those in past decades. In both children and adults, dietary and lifestyle factors appear to play an influential role in stone formation,[7] albeit within a background of genetic susceptibility.[8] Thus, Guan et al. and Wang et al. report prevalences that appear to be significantly higher than expected on the basis of data

for adults and anecdotal data for children in the United States and Western Europe.

Adults with kidney stones, as compared with those without stones, have a higher lifelong likelihood of chronic kidney disease, as judged by reduction in the estimated glomerular filtration rate.[9] Surprisingly, Guan et al. found elevated urinary microalbumin levels, a potent indicator of glomerular dysfunction, in the children with stones. The effect of such findings over a child's lifetime is unclear but would be worrisome if persistent and prolonged.

There are several caveats concerning the interpretation of the reports by Guan et al., Wang et al., and Ho et al. One cannot derive from these reports the absolute or relative risks for nephrolithiasis and chronic kidney disease from melamine exposure. The study by Guan et al., in Beijing, involves a strong referral bias, as noted by the authors, since it is not clear how many families of children who ingested contaminated formula were aware of the free screening but did not appear. In addition, the definition of a "suspected" stone is questionable and might not withstand scrutiny based on stricter ultrasonographic definitions of nephrolithiasis. Certainly, the presence of oliguria, unexplained crying, and edema in the group without stones suggests that some children were brought to the Beijing hospital for reasons beyond screening.

Guan et al. also uncovered a significant relationship between nephrolithiasis and prematurity, as well as high exposure to melamine. We know that, in general, premature infants may have high rates of kidney calcifications and nephrocalcinosis,[10] related in part to therapies used in their care and also to the relative underexcretion of urinary inhibitors of stone formation. Rates of urinary microalbuminuria are higher among premature neonates than among full-term neonates, and the condition may be persistent. Attainment of the maximal glomerular filtration rate lags in the premature infant as well.[11] Thus, the experience in Beijing may reflect combined effects of melamine exposure and prematurity on stone formation.

The report from Taiwan by Wang et al. lacks information about screening criteria. Therefore, a true denominator for calculating the rates of stone development is still elusive.

It is remarkable that all three reports describe the absence of conventional symptoms and signs related to nephrolithiasis in the children with stones. Unlike renal stones with other causes in adults and children, which commonly have well-described urinary symptoms and signs, the children with melamine-related nephrolithiasis in Beijing, Taiwan, and Hong Kong were largely asymptomatic, with detection on ultrasonography the sole indicator of the condition. Since the presence of a kidney stone is generally associated with hematuria, leukocyturia, and other urinary abnormalities, their absence in these children is unexplained. One hypothesis is that a melamine-containing kidney stone that has no proteinaceous matrix and does not react with urinary epithelium will not produce urinary findings.

How should physicians in other parts of the world care for Chinese infants who may have been exposed to melamine-contaminated powdered infant formula? The American Society of Pediatric Nephrology suggests a conservative approach in asymptomatic infants,[12] since stones presumed to have been induced by melamine ingestion appear to be passed easily after hydration, and there are currently no follow-up reports on the children studied by Guan et al. and Wang et al. Performance of abdominal ultrasonography in all potentially exposed Chinese children living in the United States would be likely to cost many millions of dollars, an expenditure difficult to justify, given that both unaffected and affected children may have no symptoms and that the meaning of a stone in an asymptomatic child is uncertain.

Without a doubt, we must safeguard our children's food supply to prevent future toxic exposures. However, the critical view of melamine exposure and nephrolithiasis gleaned from the three reports in this issue of the *Journal* raises many questions that underscore the need for intense and careful study before we know whether apparently thriving children have a major ongoing health risk from previous melamine exposure through their infant formula.

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The Growth of Hospitalists and the Changing Face of Primary Care

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Two decades ago, most doctors who chose a career as a primary care physician did not imagine a professional life restricted to the outpatient setting. The architects of training programs in primary care believed physicians would serve patients best if they developed skills to work expertly in both inpatient and outpatient settings. Thus, they designed programs with a substantial amount of training in outpatient settings, but the majority of the training still occurred in the hospital. Trainees were attracted to general medicine and family medicine for their broad scope; they enjoyed the variety of caring for healthy, acutely ill, and chronically ill patients. They also valued the opportunity to form longitudinal relationships with their patients and to be the doctor who knew them best. Few would have envisioned temporarily transferring the care of their patients to other doctors when they were admitted to the hospital — the time when patients are sickest, most vulnerable, and in need of someone who knows them, their health problems, and their preferences for care.

Today, many primary care physicians work exclusively in the ambulatory setting, relying on hospitalists to care for their patients when they are admitted to the hospital. In this issue of the *Journal*, Kuo et. al.[1] use Medicare data to describe the dramatic growth of hospitalist care from 1995 through 2006, and they estimate that in 2006 almost 20% of general internists were hospitalists. Care by hospitalists has increased throughout the United States in small and large hospitals and in teaching and nonteaching institutions. In 2006, almost half of all hospitals and 84% of teaching hospitals had at least three hospitalists. Kuo et al. also found that fewer physicians are switching fields after working as hospitalists for a short time after their residency training, a finding that suggests that the hospitalist workforce is becoming more experienced.

Among the forces that ignited and sustained the rapid growth of hospitalist care was the birth of managed care, which put pressure on primary care doctors to see more patients in the outpatient setting and on hospitals to shorten the length of stay.[2] Declining reimbursement for nonprocedural services put additional pressure on primary care physicians to see more patients to maintain their income. With the ability to manage more problems in the outpatient setting and with more hospitalized patients being treated by subspecialists (such as cardiologists and gastroenterologists) who delivered hospital-based services, many physicians were responsible for fewer inpatients. The lower volume of inpatients made it less practical for primary care physicians to block off time each day for hospital rounds and reduced their experience in the inpatient setting. By employing hospitalists, hospitals gained tighter control over clinical management, the use of hospital resources, and quality of care. In addi-