April 2015 Issue | Martha C. Morris, ScD

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Welcome to *Functional Medicine Update* for April 2015. As you know we're in our functional neurology series and we're very pleased that once again we've got an incredible clinician/researcher to help us understand this complex topic of how, in fact, functional neurological problems are developed, how they interrelate to diet and lifestyle factors, and hopefully how we can apply this information in developing personalized programs for individuals that will improve their neurological function. So this month we're going to have an extraordinary interview with Dr. Martha Clare Morris, and I think you'll be very pleased to hear what she has to say and the work that she has done in this area, so let's shift to our discussion with Dr. Morris.

INTERVIEW TRANSCRIPT

Researcher of the Month

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So here we are once again at this—for me—the most interesting part of our Functional Medicine Update each month, and that's our clinician/researcher of the month section. As you know we have been involved in the last few months with this development of a functional neurology focus. We've really done a nice job, I think, of looking at the molecular mechanisms that are prevalent as it pertains to the origin of conditions like Alzheimer's disease and Parkinson's. We've had a review of some of the more recent literature that really talks through the eyes of the investigators and their experience about some of

the pros and cons of the new approaches that are being considered for the prevention and treatment of neurodegenerative diseases. We've had some very interesting discussion about the multiple risk factor components, including apoE4 alleles and the relationship also to things that pertain to metabolic inflammation and its association with neurodegenerative conditions.

And that leads us up to what today I think is kind of the payoff for a lot of this investigative discovery work that we've been exposed to over the last several issues, and that's the work of Dr. Martha Clare Morris. Dr. Morris is at Rush University. She is an associate professor in the Department of Internal Medicine and the Rush Institute for Healthy Aging. She is also the assistant provost for community research and the director of nutrition and nutrition epidemiology at Rush University Medical Center. She received her Bachelor's and Masters of Science in Sociology at the University of Iowa and her doctorate in epidemiology at the Harvard School of Public Health. Her work is just, I think, really very interesting because it covers quite a large breadth of topics that have been the focus of what we've been speaking to for 30-plus years in Functional Medicine Update, dealing with nutrition, lifestyle, risk factors that relate to public health-related issues, and then focusing, in cohort analysis, down to individual, say, presentation types and genotypes. Dr. Morris has a rich publication record that I think reflects very, very nicely the topic that we have been focusing on as it relates to functional neurology and how that really translates directly into communities, populations, and ultimately obviously to individual people.

Dr. Morris, it's really a privilege to have you on Functional Medicine Update and thanks so much for being available for our discussion.

MM: Thank you. I'm very honored to be a part of your show.

JB: Let's just start off with some general thoughts. I was very intrigued to look at the department you've been a principal in at Rush: the section for nutrition and nutrition epidemiology. How did that originally get started at Rush University? It sounds like a very interesting cross-disciplinary department.

University Department Focuses on Nutrition, Aging, and Neurodegenerative Disease

MM: Yes, well, I've been doing research in this field of aging and dementia for over 20 years. Here at Rush we have a very vibrant group that has focused on community studies, looking at people without dementia living out in the community, and looking at what factors might determine who gets Alzheimer's disease, who has cognitive decline with aging, physical decline with aging. Our group has been very active in this area for a long time. I had a specific interest in nutrition and had received training at the Harvard School of Public Health and Nutritional Epidemiology, and started a focus within our group to look at how diet might impact cognitive aging and the development of neurologic conditions with aging, like Alzheimer's and Parkinson's and stroke and other conditions.

At the time that I started this there was really, you know, no activity in the area of nutrition and neurodegenerative diseases. It was wide open, so I really focused my attention, then, just on looking at the most likely diet components that would protect the brain, and really had to focus on just a few animal models. There was nothing else in the literature to guide me in my research. As I got more and more focused in this area, I split off from my group and started this section that was devoted to nutrition as it relates to aging and neurodegenerative diseases. And it's very new; it's only about five years old or so.

JB: I notice that you're also the co-director of the Translational Science Consortium, which—to me—sounds really interesting. It's like taking information and finding a way to go from, maybe, bench to bedside, or having direct application. How does that fit into this whole activity that your department is involved with?

MM: That's more of a university-wide effort, and it has been a new direction of science in the last six or seven years. Rush University, where I'm located, has some, you know, very translational-focused areas, including in neurodegenerative diseases, where laboratory work at the cell level and with animals is related to our community study work, where hypotheses that are generated in the animal laboratories we can then integrate in our community studies, and vice versa—as we see relations with diet and neurodegenerative diseases in our population studies, that can be taken back to the laboratory to try and understand mechanism. That's just an example of neurodegenerative disease, but we also have areas of focus at Rush around biochemistry, and orthopedics, and bone metabolism, for example, is another area. So I sort of have two hats, one where I focus on nutrition as it relates to aging, and also trying to develop this science university-wide of trying to get science to be more efficient and quicker at taking laboratory ideas and getting them into practice in the community.

JB: That really deserves applause. I think that is a growing trend and I think it's a fortunate trend because there is a lot of extraordinary information and discoveries out there that really haven't found kind of translation into practice with the speed at which we'd like, so congratulations. Let me, if I can, move to some specifics related to your work. I was really intrigued—I'm intrigued by all of your publications, but one that was in 2014 that appeared in the Journal of the American Medical Association I thought was very topic titled "Vitamin E, Memantine, and Alzheimer's Disease."[1] And, of course, Namenda being a trade name for a new Alzheimer's add-on drug. This was looking at a specific trial that had been published in JAMA by Dysken et al. that looked at the effects of Namenda along with vitamin E in Alzheimer's disease. Could you tell us a little bit about your editorial? Because I thought it was very, very insightful in terms of the way that you were evaluating outcomes from that study.

Could Vitamin E Supplementation Slow the Progress of Alzheimer's Disease?

MM: Yes, so it was a very interesting study where pharmacologic doses of a vitamin E supplement (2000 International Units) helped to slow the need of Alzheimer's patients to use the help of caregivers in their daily activities, which is really, I think, a phenomenal result.[2] And it's the second such study that has shown that. But all in all, the studies of interventions—pharmacologic interventions—with Alzheimer's disease have been fairly disappointing, so we were trying to highlight that preventive measures and focus on research and prevention of Alzheimer's is so critical because, number one, there is no cure to date for Alzheimer's and the treatments are largely…in fact, this was an unusual result from this trial. And the results were mild. It wasn't a reversal of the disease at all, it was just slowing the progression some.

JB: And in your editorial you talk about the negative interaction between alpha tocopherol vitamin E, which was—as you mentioned—significantly beneficial alone, and memantine. I think that raises some questions about do these combination of drug and nutrient intervention trials produce results that might be skewed as a consequence of the adverse interaction between the components. It was kind of an interesting observation.

MM: Yes, it highlights that we can't just assume, "Well this trial showed this drug to have some

favorable outcomes, and this drug has some favorable outcomes, and if we put them together they'll be even better." So we have to be very cautious in what we mix (what drugs we mix) to try and treat a disease.

JB: This work plays off a body of work that really, in your group, preceded it and was really pioneering in the evaluation (the epidemiological evaluation) of the role of antioxidant nutrients and the risk of incident Alzheimer's. I recalled a study that I think you were a principal author of that appeared in JAMA back in 2002 that looked at dietary intake of antioxidant nutrients, and I think made some discoveries as it relates to which (if any) antioxidants might be most valuable as it pertains to Alzheimer's.[3] Could you tell us a little bit about that work?

MM: Yes, so we have a community study, which ultimately—over more than 20 years—we had more than ten thousand people from the community participating who were 65 years and older. We did a comprehensive assessment of the diets of participants in this study and related the diet intake to the development of Alzheimer's disease. One of the first nutrients that I was interested in looking at was vitamin E because it is one of the more potent antioxidant nutrients. There have been quite a few animal models that found that either deficient levels of vitamin E or supplemented vitamin E prevented—in these animal models—memory dysfunction and showed decreased neuropathology in the brains of these animals. I looked at the vitamin E intake from food sources as well as total intake from food and then multivitamin and individual vitamin E supplements. What was very interesting was that it was the food intake of vitamin E, not the supplements, that reduced the risk of developing Alzheimer's disease. And that finding has been replicated in numerous other community studies where either you measured in the diet or measured in the serum, which would be a more objective measure of diet. So that's very interesting. We also looked at vitamin C and found no relation between vitamin C and incident Alzheimer's disease, which is also a finding that has been replicated in other studies.

JB: And I think you also looked at beta-carotene, as I recall, as well, and did not find an association with that either, is that correct?

MM: We did not. Now, at the time that we conducted that study, there was no beta-carotene supplement used. What is interesting is that there has been—since that time—a randomized, controlled trial that looked at beta-carotene supplement use. It was in the Physicians' Health Study. They checked on assessments of cognition after a long period of time that the physicians were on this beta-carotene supplement. And they found that the supplement use—the beta-carotene supplement use—decreased cognitive decline in this clinical trial of the physicians.[4]

JB: That's very interesting. With regard to what you observe with the difference in outcome of the food-based vitamin E intake versus the supplement intake of vitamin E, do you believe that the vitamin E from the food was a surrogate marker for a range of other, say, phytochemicals that come along with foods that are rich with vitamin E, or can we say that it was really the kind of complex nature of a natural mixture of vitamin E and food, or we don't know the answer to that question presently?

Examining Food Sources versus Supplement Sources

MM: We can only surmise what would explain that. There are many differences between food sources of certain nutrients—vitamin E, in particular, I can talk about—and the supplement sources. So one difference

is that when you consume vitamin E in the diet, there are different forms of vitamin E, and our diet actually contains more gamma tocopherol, and gamma tocopherol is more common in the US diet, whereas alpha tocopherol is the form that is used in vitamin supplements. So the form of tocopherol is one difference between the food sources and the supplement sources. Another difference is dose level. The dose level that you get from vitamin supplements can be up to sixty times the level that you consume through diet. The body modulates very strictly the levels of vitamins in our system. So taking a very high level of one type of vitamin can cause things to happen in the body that you might not expect. For example, there have been some experiments to show that taking of high dose alpha-tocopherol decreases the body's absorption of gamma tocopherol, and gamma tocopherol is a very potent anti-inflammatory. So by taking these supplements, we're throwing our body off on other things that would not happen had you consumed the nutrients through food sources.

JB: That's very interesting. I noticed also in your JAMA work that you found that the association between food vitamin E and the reduction in the decline, as a consequence, of Alzheimer's was not seen in those individuals that had apoE4 alleles, is that correct? So it didn't seem to be able to modify that expression function in the apo E4-carrying individuals?

MM: Yes, we did report that result, however I don't believe that that result has been replicated, and so it could have been just a chance occurrence. So it's important to see that a finding in a study is repeated a number of times in other populations by other investigators. Things do happen by chance and it just might be that that was a chance finding.

JB: So let's talk about the whole nature of the RCT evaluation of dietary supplements and conditions that are associated with neurodegeneration or maybe just chronic disease at large. You were a co-author with Christine Tangney of a really interesting editorial, I thought, in the JAMA. This appeared in 2011, April 6 issue, titled "A Potential Design Flaw of Randomized Trials of Vitamin Supplements."[5] I think it is really worth our listeners understanding your evaluation because I think it was very well said and very on target. Could you tell us what led you to write that editorial and what your thoughts were?

Randomized Trials of Nutrients Are Flawed in Design

MM: Sure. There's a lot of controversy around this area. There are many proponents within the nutrition and nutritional epidemiology world that are highly critical of the randomized trials that have been conducted to test nutrient associations with chronic disease. The model used in these randomized trials is more of a medical model, where you take the nutrient, you put it in a supplement like a drug, and administer it like a drug, which is really antithetical to the way the body metabolizes nutrients, and we talked about some of the issues: the idea that in food sources contain many different biochemical components of a nutrient at very different dose levels than what the supplements are. But what I was highlighting in the article that you mentioned was another type of problem with these randomized trials, and that is in the epidemiological studies that find these associations with nutrients and the development of disease, oftentimes it's looking at people who have high intake from food versus marginal or very low intakes of the nutrients from food. And then the randomized trials completely ignore this in the design of the trial. So basically they are recruiting people into the trial who already are at the highest level of food intake to give them the best physiological benefit. So by giving them even greater amounts of that nutrient, they're already at the 100 percent level for functioning, so you can't improve them further.

JB: I thought it was very powerful. You described the three randomized clinical trials at the time you wrote this article on vitamin E in cognition and you point out that none of these trials targeted individuals who had low dietary intake and in fact they probably didn't stratify at all for diet intake in terms of the effects of supplements in those individuals.

MM: Right. Now the Europeans have done a better job at designing their diet intervention trials, their nutrient supplements. There is a clinical trial that was done in The Netherlands called FACIT, where they did target people that they recruited into the trial who had suboptimal—they had marginal—folate status based on a number of diet and biochemical measures. And they had higher homocysteine levels, and there was no other reason from their biochemical analyses, other than low folate intake for the high homocysteine. And they, then, randomized them to receive the folate folic acid, which is a synthetic form of folate, or a placebo, and after three years the folic acid group did have a reduction in cognitive decline compared to the placebo group. So that's an example of a well-designed trial that we have not done in the United States.[6]

JB: Yes, and I think that really raises some—as you pointed out—very interesting questions about the complex nature of foods. Let's take an example with folic acid, as you just mentioned, because we know that folates can be in all sorts of polyglutaminated forms. We know that there is 5-methyltetrahydrofolate as well as folic acid itself. So there are multiple congeners of these bioactive nutrients that may have all sorts of pleiotropic effects on function. Often if we just give a folic acid supplement alone we're missing that symphony of actions that might occur from the full-food form, I think is what you're leading us to understand.

MM: Yes, and actually folic acid has another issue in that it's a cofactor nutrient in a very complex metabolic process, along with vitamin B6 and vitamin B12. And based on a number of studies now, there's this concern that folic acid supplementation in individuals with low vitamin B12 status actually accelerates neurodegenerative decline, including loss of cognitive function. Diet is just such a complex process, and you really have to be careful by supplementing.

Studying the Mediterranean Diet and Cognitive Decline

JB: So let's move over to some of the recent work that you've done in the area of diet and its relationship cognitive decline. I think that this growing interest in different types of dietary patterns and their interrelationship with cognition and other chronic diseases is very fascinating. One of your recent papers appeared in the Journal of American Clinical Nutrition: "Adherence to a Mediterranean-Type Dietary Pattern and Cognitive Decline in a Community Population." This appeared in 2011, page 601.[7] I think that this is one, again, of a number of studies that have been published from different investigators recently that seems to pinpoint some beneficial effects of a Mediterranean-type dietary pattern and the prevention of cognitive decline. Can you tell us a little bit about this work?

MM: So this is a fairly new focus of nutrition and dementia. The evidence isn't as consistent as one would like for the Mediterranean and other diet patterns, but there are some methodological issues in the way people have tested these different diets that perhaps have confused the picture. We looked at the Mediterranean diet as well as the DASH diet, which is a very well documented diet that is effective in lowering blood pressure, reducing diabetes incidence, weight gain, so the DASH diet has a very strong cardiovascular history of being protective for cardiovascular disease, as has the Mediterranean diet. In

two of our community studies, now, we have found that both of these diets reduce cognitive decline with aging. We've developed this area even further. Just recently we had a publication that came out just last week where we took a hybrid of these two diets, but then modified them to reflect the literature that is specific to diet and the brain, because the Mediterranean diet, after all, is a cultural-based diet that has been related to cardiovascular disease. And DASH was originally designed for hypertension and, you know, cardiovascular conditions. So we tried to build upon those diets by specifying certain foods and modifying them somewhat to reflect the dementia literature. And we found stronger associations—more protection—with this MIND derived diet than either the Mediterranean or DASH diet.[8]

JB: That's really fascinating. You know we had the opportunity to interview, some years ago, Dr. Suzanne Craft, who was then (at that time) at the University of Washington and the VA center related to aging. She had made some very strong observations and published her work on the insulin-associated (hyperinsulinemic association) between Alzheimer's and how that related to prevention through a low glycemic load diet, so she was very strongly encouraging a major determinant would be glycemic response to foods and how that would enhance insulinemic activity. Do you feel, from your work, that there is more to the story than just the insulinemic response or is that a major component of this benefit you're observing?

Biomarkers at Mid-life May Relate to Development of Alzheimer's in Late Life

MM: So there has been very, very limited study in the area of glycemic load/glycemic index/the glycemic diet in relation to the development of dementia, so it's very difficult to make a comment one way or the other with such limited study. Certainly there is an interesting biological mechanism by which it may, in fact, be a factor (a diet factor) that could help to prevent the disease, but we just need more studies, more research, to look at this carefully. I think one of the problems with this study is that we find, when we look at older populations, there is Alzheimer's dementia brain change effects on metabolic factors. Blood pressure is an example. Obesity is another example. Hypercholesteremia is another example. When you look at the studies that have looked at those factors in relation to development of dementia, typically there is no association found. It's only when you go back to the middle age years and you look at who has hypertension, who has hypercholesteremia, who is obese in their middle years, and then they relate those factors to the development of this dementia in late life—it's only those long-term studies that have found association. Probably what is occurring is that the brain and the changes that it is going through is affecting the level of blood pressure in late life, the level of cholesterol in late life. It is very likely that the same thing is going on with the diet factors.

JB: Very interesting, so when you developed this hybrid between the DASH and the Mediterranean diet and picked up certain foods that were to be emphasized, were those foods high phytochemical or nutrient dense-related foods? What were the principles by which certain things were emphasized?

The MIND Diet: A Hybrid Approach

MM: I can tell you what some of the major modifications were. For one, both the Mediterranean and the DASH diet specify four to five vegetable servings per day. In the literature on vegetable intake and the risk of cognitive decline in particular, it's really very specifically green leafy vegetables that are important, so we built into our MIND diet score a separate component apart from other vegetables, green leafy vegetables. This literature seems to indicate that almost a serving of green leafy vegetables a day is

associated with slower decline. That was one thing that we changed. Another component is the fruit component. Both the DASH and the Mediterranean diet specify about four to five fruit servings per day. Well, in the dementia field, fruits as an individual category have not been associated with cognitive decline or risk of developing dementia. There is, however, a very strong animal literature, and one or two epidemiological studies that have shown that berry in particular—that single type of fruit—is associated with neuroprotection. So we did not specify four to five servings of fruits per day, we specified—several times a week—berry consumption. Those are two differences, and then the Mediterranean diet specifies six or more servings of fish per week. The DASH diet really doesn't focus on fish. The literature in the dementia field really shows that the level of benefit from fish for developing Alzheimer's of cognitive decline is at one fish meal a week. There is little to indicate that consuming more than one fish meal a week is even better, so we modified that component of the MIND diet to just one fish meal a week. So those are several of the types of modifications that we made. Certainly we do have a separate component for vegetable servings, but green leafy vegetables, berries, other types of vegetables—those are all very high in micronutrients and phytochemicals. So, yes very high micronutrient phytochemicals in the diet.

JB: Taking this extraordinary breadth of work that you've been involved with for these many years, and kind of doing the broad brush—moving up to, say, the 30,000 foot level—what is your kind of view as it relates to how we're going to fight back against this rising tide of Alzheimer's and other non-Alzheimer's dementia, which is certainly becoming the big health-related risk and functional problem in our culture. What's your crystal ball say so far from the work that you've see and been involved with?

MM: One of the more important things, I think, is to have a diet intervention randomized trial. Prevention is so important for fighting this disease at the public health level for the reasons that I mentioned earlier—that right now we don't have a cure, there really hasn't been a new drug on the market for many years now, and they are really largely ineffective anyway. So prevention can do so much. They've shown that just delaying the onset of Alzheimer's disease by five years can have on the financial burden, the resources required to live out the disease, it can have a really significant impact, so preventive factors really need to be studied vigorously. So far there have been randomized trials of physical activity to prevent the disease, cognitive activities, social activities, meditation, yoga; there hasn't been one diet intervention trial. We're working very hard to try and make this a reality. Then there can be public health messages and recommendations. If we have a full diet intervention trial, the Alzheimer's Association, the National Institute on Aging can put out there, you know: "Here are the foods and the type of diets that can help you to prevent the disease."

JB: There is one thing that struck me as very interesting in your work, and that was the association between wine consumption and neurodegeneration (inverse response) and the suggestion that maybe this has something to do with phytochemicals like resveratrol, but it may have an alcohol-related effect as well. What has been the dominant theme about alcohol consumption and neurodegeneration at this point.

MM: So if I understand your question it is what component in wine consumption, is that what your question is?

JB: I think my question is, first, is this inverse association between alcohol consumption—modest alcohol consumption—and neurodegeneration seemingly replicable, and if so is there a difference in the type of alcohol consumed and the influence it has on neurodegeneration?

MM: My focus hasn't been on alcohol consumption. I believe, from what I know of this literature, there are associations with other types of alcohol being protective in addition to wine. Wine has been vigorously studied because of the resveratrol. There have been hypotheses that the social nature of drinking alcohol might also be a component associated with alcohol consumption that related to lower risk of getting Alzheimer's disease because social interaction has been one of the factors that has been shown to be important for reducing your risk of getting the disease. So it's hard to pull apart what drives the alcohol association as a protective factor, but what is so important to emphasize is that the level of benefit—the protective level of benefit—is very low. No more than one glass of alcohol—you know, a glass of wine for a woman and no more than two for a man—is what we observed in the studies. So there is this concern of people taking that to the next level and increased amounts of alcohol are very neurotoxic; they can cause dementia. It's a two-edged sword, there.

JB: Yes, I think again that goes back to your comments that you made in your editorial—the potential design flaw, where you talk about the inverted U effect of many things, that what may be beneficial at one level can turn opposite and become a hazard at another level. Kind of the shape of that parabola determines the relative safety margin for that particular substance.

MM: Well put, yes.

More Studies are Needed on the Role of Carbohydrates in Dementia

JB: Let me just ask one last follow-on question. We often hear debates about the nature of carbohydrate in the diet and whether this is a contributor to dementia in the long term and of course there are all sorts of different ways that carbohydrate can be consumed, from simple carbohydrate sugars to highly refined white starch in either amylopectin or pectin, or we can look at even the unrefined, fiber-rich, nutrient dense types of carbohydrate. What has your work in looking at carbohydrate connection told us? Is there a difference between the complex, minimally processed, whole grain carbohydrates than that that is highly processed?

MM: There has not been adequate study in this area at all in relation to brain changes with age and the development of dementia. It's very limited and that is one area of study that really needs to be developed. It does have the same type of problem that I mentioned before with glycemic index and glycemic load. We may observe a different relation in studying older people than we would if we went to the middle aged years and looked at simple carbohydrate intake versus whole grains and more complex carbohydrates in relation to the development of dementia and brain changes with age. This is a field that has very few studies that have published on it.

JB: So let me ask you the last question and that is most of the listeners of this discussion between us will be healthcare providers and they are undoubtedly being asked by patients what should they do if their parents, or loved ones, or colleagues were in this state of Alzheimer's. They may either in their own lives do something to prevent or to provide the proper advice to their patients. What would you do in that particular situation if you are sitting knee-to-knee with a person asking you what is the best approach?

MM: I would take the approach from two perspectives. One is that we know that a lot of the factors that protect or lead toward increased dementia are the same factors that are heart healthy factors, so we don't know with assurance that some of the factors that look to be protective or harmful for dementia are indeed

so, but if you follow the heart disease world, you're going to be hitting a lot of those factors. If you are a caregiver of somebody who already has Alzheimer's disease, the approach from the diet perspective might be to be sure that the diet is more similar to the Mediterranean of the DASH diet, or you can look up this new publication on the MIND diet, which was published in Alzheimer's and Dementia. So you can be sure that their diet is, you know, of the healthier variety, but in addition I think it is very important for anyone who is aging (middle adult to later years) to have biochemical analyses done to determine whether certain nutrients are low. What is your B12 level? What are your vitamin D levels? What are your vitamin E and folate levels? It may be that you, as an individual, are in the marginal status, and then it might be appropriate to take a supplement to correct that marginal status. So I think those two approaches will take you a long way to protect your brain dietarily.

JB: We can't thank you enough for the years of effort that you put into this field and the work that you have published, and also with taking a very complex topic that has still a lot of questions yet to be answered and making sense of all this has really been a great journey you have kind of guided us through here. I think the encouraging thing is it seems like at least people are starting to ask the right questions now. You can't ever get an answer unless you ask the question and it seems to me, with the quality of work that's being done in your group and others, that we're finally starting to at least design studies that will allow us to have answers to questions that have been sitting around for some time without understanding. Thank you very, very much. I think you've given us a tremendous amount of news to use and we wish you the very best in your continued work and we'll be following it very closely.

MM: Thank you very much. It's been my pleasure.

JB: Thanks so much.

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