Commentaries

Dovenning

There is a pejorative term for intellectual time-wasting in Jewish medical circles, called "dovenning," which means "praying while standing and swaying to and fro" in Hebrew. One example would be a protracted discussion on the efficacy of various chemotherapeutic trials on a 95-year old demented person with metastatic cancer. Exercises in verbosity, the showing off of useless knowledge, the recitation of knowledge and the exercise of useless decision-making algorithms when the answer is obvious, without having education as the real motivation.

I read an article recently about an experimental intervention on an animal model of **Huntington's disease (HD)** which made me think that all the seemingly meritorious work that many of us, and I include myself, are involved in trying to develop some treatment for this dread, incurable, inherited disorder represents useless money-wasting, or dovenning. More importantly, this observation applies far and wide, and, to a large degree, we all know it, even if we don't acknowledge it. In this case a drug was given which detoxified the abnormal HD protein. So, instead of figuring out what the protein did, or how to block gene expression, a different approach yielded a great benefit. Will this work in the "real" disease, that is, in humans? It will take time to find out, but the approach is plausible, and could, theoretically prevent disease expression.

The gene for HD has been known for over a decade. It's been expressed in a variety of genetically-engineered rodents who then develop some of the phenotypes of HD along with similar brain pathology. The abnormal protein causes poisoning of the involved brain cells, although how it does so and why it does so only in certain nerve cells and not others, although it is widely expressed, remains unknown. Since the gene abnormality in HD causes a "gain of function" toxic state, rather than a "reduced-function impairment" due to insufficient gene expression, HD can be prevented if the gene expression can be stopped. Through mechanisms related to mRNA interference, chemicals have been developed which stop or reduce expression of the abnormal gene, hence reducing the abnormal gene product, thereby reducing the pathological changes of the disease in the rodent brain. This is clearly how this disease and many, perhaps most, other genetic disorders are going to be halted, hopefully even prevented. Yet we are spending millions of dollars on studies related to incremental advances in disease modification pursuing large, expensive clinical trials testing a drug that may alter mitochondrial function which might be the pathogenetic mechanism but for which there is no direct supportive data. Perhaps we've learned the wrong lesson from cancer trials.

We now devote millions to study how the first symptoms of HD manifest, by studying the children of people with HD; and on studying mitochondrial-boosting drugs (coenzyme Q 10 to be specific) to slow disease progression.

In other neurodegenerative disorders we are making similar investments, often with less scientific rationale, making educated guesses at disease mechanisms to design trials of drugs to alter disease progression, some producing minimal benefits. But we perform other studies of questionable benefit as well. I recently listened to a discussion on weight loss in **Parkinson's disease (PD).** It is common for PD patients to lose weight. For many patients this is not a problem. It becomes easier for them to stand up and walk. It is easier for their spouse to help them get up if they fall. On the other hand it sometimes reinforces a psychological feeling of everything going downhill and it may cause increasing weakness. There are many potential reasons for weight loss: depression, apathy, slowness of chewing and swallowing, dysphagia, dry mouth, loss of olfaction and taste perception, the social difficulties of taking so much longer to eat than others, and likely untold other reasons. Is it important? I think not. In any patient it could be due to any of the explanations, each with a unique profile of the importance of each explanation. I care about my particular patient, because it is important to exclude cancer, diabetes, hyperthyroidism, etc, and to treat depression, but I doubt that figuring out a generic cause for weight loss in PD is of any value. What value will that have?

There is a lot of well done but useless research being published. When reviewers score manuscripts. they grade not only the quality of the work, but also its importance. I think that reviewers are more attuned to grading the quality of the work than its impact. I am not concerned here with reports that have limited relevance. Most doctors are not interested in extremely rare disorders which they will never see or treat, but where the discovery is still relevant. I am more concerned about studies where something is measured that has limited importance. For example, will it matter if weight loss in PD is due to slow eating or early satiety, or reduced interest in food? The bottom line is weight and what can be done to increase it, if it's a problem; and that always calls for more calories unless there is correctable mal-absorption. The increase in intake might occur with richer food, drugs to enhance appetite or foods that are easier to swallow, but we generally approach the problem with all three.

I reported rhinorrhea as a feature of PD. Is it irrelevant, or, as an old college friend would say, "Joseph, Ask me if I care." It does matter, because it is common and patients like to know that it is part of their disease and it saves useless (and expensive) tests and referrals, and is treatable. It also is another, albeit common, premotor sign of PD that may ultimately be used to identify those at risk of developing the motor symptoms of the disease. Although one could argue that, like weight loss, it can be treated without understanding its etiology, it is clear in PD that when neither doctor nor patient recognize it as a part of the disease, it gets neither recognized nor treated. Unless asked about it, the usual inference of a PD doctor to a patient carrying a tissue is that it is used for drooling or tearing, when, in fact, it is for runny nose, unrelated to allergies, in about half the cases. Certainly no one died of rhinorrhea, but quality of life often hinges on non-serious issues, including not being able to eat in public due to a nasal drip.

We need to focus on using our resources wisely. Wasteful clinical projects should not be funded simply to make people with the common diseases feel that they are getting attention. On the other hand the money needs to be used on these diseases, just used more wisely, and not shifted to other areas.

It is good to know things. But some things are more important to know than others, and our exponentially-expanding number of medical papers needs to be contained. There used to be a satirical journal for scientists, *The Journal of Irreproducible Results*. It may be time to establish a number of journals in various medical disciplines, each called, *The Journal of Irrelevant Results.*

– Joseph H. Friedman, MD

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