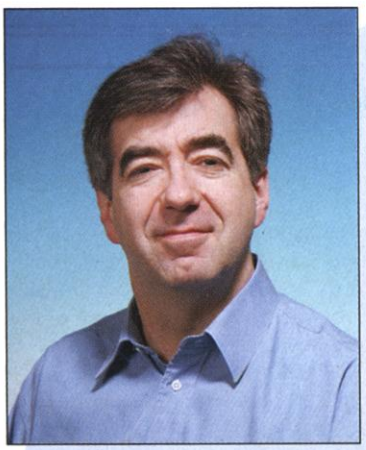
Dwek, along with Oxford colleagues Terry Butters and Frances Platt, reasoned that they might be able to restore the body's glycolipid balance—at least in patients whose mutations don't completely destroy the affected enzyme—by decreasing the synthesis of the glycolipids, which also occurs in the ER. This time, they chose a sugar variant called NB-DNJ as their weapon of choice. The results have been promising. "We don't shut down glycolipid synthesis completely, just enough to restore the proper balance between synthesis and degradation," says Dwek.

Oxford Glycosciences, an Oxford, U.K.–based biotech firm specializing in carbohydrates, has been conducting clinical trials with NB-DNJ, known more prosaically as Vevesca, both alone and in combination with Cerezyme. Last April, the company published initial clinical data in *The Lancet* demonstrating the drug's safety and hinting at its effectiveness. Last month, the company announced its preliminary analysis of a 6-month phase III study indicating that the compound—which is taken orally—was as effective as Cerezyme at maintaining healthy phospholipid levels. With these promising results in hand, the company is now pressing forward with clinical trials on related compounds for other lipid storage disorders, including Fabry's disease.

This new surge of interest in carbohydrate-based therapies is removing some of the sour taste of the earlier disappointments in the field. Now, glycobiologists are more confident that a spoonful of sugar will not only make the medicine go down, but replace it with something that works better.

–JOSEPH ALPER

Joseph Alper, a science writer in Louisville, Colorado, is managing editor of the online biotechnology magazine *dailytwist*.



Protein pioneer. John Collinge argues sugars may misguide protein folding.

PROFILE

Bent Out of Shape

LONDON—When it was first proposed in the early 1980s, the notion that aberrant proteins called prions can replicate without DNA or RNA and cause infectious diseases was biological heresy of the first order. While still controversial, this hypothesis eventually won enough adherents that it earned its leading advocate, University of California, San Francisco, neurologist Stanley Prusiner, the 1997 Nobel Prize in physiology or medicine. Now, John Collinge, a neurologist at St. Mary's Hospital in London, is pushing the controversy a step further. Collinge contends that the differences between prion types, or "strains" as they are often called, is in large part determined by how many carbohydrate molecules bind to a protein. This claim has helped make Collinge one of the prion world's most high-profile scientists.

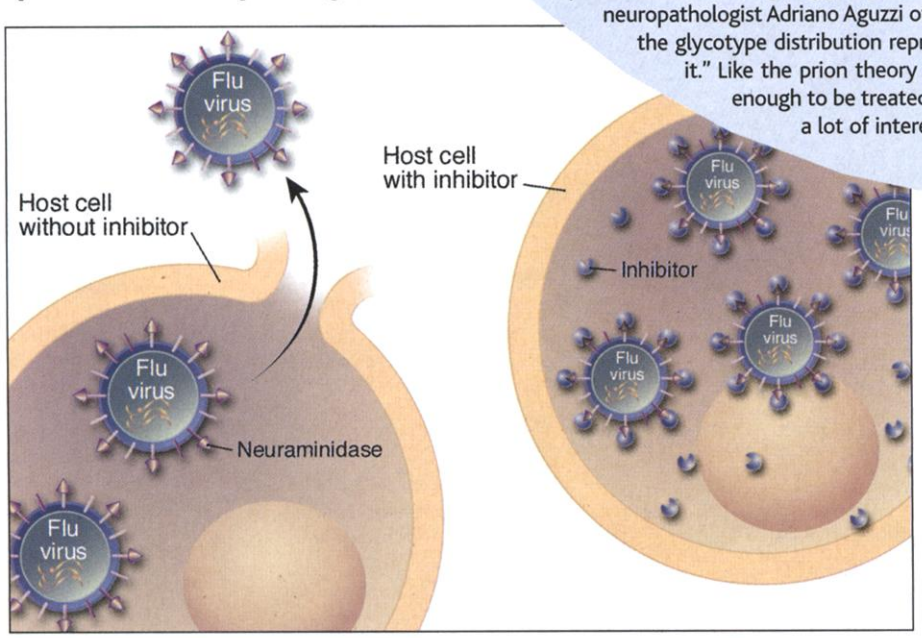
Collinge was introduced to prion diseases in the late 1980s when, soon after medical school, he began working in psychiatrist Tim Crow's lab at the Clinical Research Centre in Harrow, U.K. Shortly before, Crow's group, together with Anita Harding's team in London, had identified a gene mutation linked to an inherited form of Creutzfeldt-Jakob disease (CJD), an invariably fatal neurodegenerative disorder. Other workers had showed that this gene codes for a protein called PrP, of which prions are misfolded versions, and Collinge set to work characterizing this and other PrP mutations responsible for CJD. According to Collinge, the fact that the prions created by these mutations could then infect experimental animals was a "very powerful argument" that proteins alone could cause a transmissible disease.

In 1990, Collinge moved to St. Mary's, where he continued working on prion protein genetics and structure. Other researchers—including Richard Marsh of the University of Wisconsin, Madison, who worked on prion diseases in minks—had found a correlation between prion strains and protein structures. Collinge's group, working with the prions that cause human disease, found that strains also correlated with the pattern of sugar groups bound to the protein. For example, prions isolated from the brains of patients with "classical" forms of CJD were found to have a very different sugar pattern from those isolated from patients with a variant form of CJD that struck some patients much earlier in life. But the sugar pattern of variant CJD prions was identical to those that cause bovine spongiform encephalopathy—a finding key to establishing that variant CJD was in fact the human form of "mad cow disease."

Collinge believes that sugars known as glycosyl groups mark prion strains in part because they stabilize the proteins' aberrant shapes. "Certain [protein] conformations will associate with different glycosyl patterns," he says. And in early 1999, Collinge and his colleagues reported developing a diagnostic test that detects variant CJD in tonsil biopsies on the basis of their glycosylation patterns (*Science*, 22 January 1999, p. 469).

Given the continuing controversy over whether proteins alone can form infectious particles, many of Collinge's colleagues are intrigued but cautious about the role of sugars in prion diseases. Collinge's glycosylation work "is a very significant breakthrough," says neuropathologist Adriano Aguzzi of the University of Zurich. "But we do not know if the glycotype distribution represents the essence of a strain or a surrogate for it." Like the prion theory itself, Collinge's glycosylation theory is heretical enough to be treated with caution but intriguing enough to stimulate a lot of interest.

–MICHAEL BALTER



No escape. Newly approved carbohydrate drugs block the ability of flu viruses to exit infected cells by binding to neuraminidase, a viral protein required for the job.

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