olive oil was 22.0% in the group receiving extra-virgin olive oil (vs. 16.4% in the control group); the average energy intake from nuts was 8.2% in the group receiving mixed nuts (vs. 1.6% in the control group). Those in the group receiving extra-virgin olive oil modestly decreased consumption of regular olive oil but replaced it with even greater amounts of extra-virgin olive oil.

The reduction in cardiovascular disease was most evident for stroke, an outcome that is exceedingly dependent on blood pressure. This result is concordant with those of observational studies, which have shown that Mediterranean-style diets and olive oil are associated with reduced risk of stroke.[6-8] Previously, the PREDIMED investigators reported that, at 3 months after randomization, the group receiving extra-virgin olive oil and the group receiving mixed nuts had substantially lowered blood pressure.[9] Indeed, reductions in blood pressure probably contributed to observed reductions in cardiovascular disease. However, the effects of the interventions on known blood-pressure determinants (i.e., weight and dietary sodium and potassium intake) are unknown.

The impressive results of the PREDIMED trial confirm that changes in diet can have powerful, beneficial effects. But what are its policy implications? The PREDIMED trial is neither a pure test of a Mediterranean-style diet nor a pure test of extra-virgin olive oil and nuts. Interpretation of the PREDIMED trial is similar in complexity to that of the Lyon Diet Heart Study, which tested provision of a margarine rich in alpha-linolenic acid, coupled with brief advice to consume a Mediterranean diet.[10]

Policymakers[1] already recommend consumption of a Mediterranean-style diet on the basis of a persuasive body of evidence from observational studies. Our sense is that the policy implications of the PREDIMED trial relate primarily to the supplemental foods. Specifically, in the context of a Mediterranean-style diet, increased consumption of mixed nuts or substitution of regular olive oil with extra-virgin olive oil has beneficial effects on cardiovascular disease.

Still, there are many unanswered questions. Will the benefits of extra-virgin olive oil and mixed nuts accrue to persons consuming other diets? Does high consumption of extra-virgin olive oil and mixed nuts lead to weight gain? Can the benefits of extra-virgin olive oil and mixed nuts occur at lower doses?

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore (L.J.A.); and the Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago (L.V.H.).

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Efficiently Killing a Sugar-Coated Yeast

John R. Perfect, M.D.

With the inclusion in this issue of the *Journal* of the study by Day et al. on the treatment of cryptococcal meningitis,[1] the *Journal* has provided the medical community with a trilogy of studies for the understanding of combination therapy with amphotericin B and flucytosine for cryptococcal

meningitis. In 1979, Bennett et al. provided the first results showing the value of this combination regimen, as compared with amphotericin B monotherapy, and validated its fungicidal properties.[2] In 1997, van der Horst et al. described the success of 2-week induction therapy with amphotericin B plus flucytosine for cryptococcal meningitis in persons with human immunodeficiency virus (HIV) infection.[3] The present study shows the superiority of the combination therapy over monotherapy with respect to both direct antifungal activity and survival. The results confirm that this combination is the preferred regimen for the induction treatment of cryptococcal meningitis. This recommendation has been codified in the 2010 guidelines from the Infectious Diseases Society of America.[4]

These studies provide an evidence-based framework for the value of combination antifungal therapy. In clinical medicine, we frequently are challenged with the simple concept that a combination of antimicrobial agents may add benefit. For instance, if one antimicrobial agent works, then two or three agents may provide an additional therapeutic benefit. We have become enamored of the success of highly active antiretroviral combination regimens, but except for a few bacterial infections, combination antimicrobial therapy is driven by the hope for broader coverage and reduced development of drug resistance rather than by the demonstration of improved potency and outcomes. However, this study with amphotericin B and flucytosine shows a benefit that has been based on years of in vitro studies, animal models, and clinical studies.[2,3,5,6] In cryptococcal meningitis, the principle is set: the rapid killing of yeasts at the site of infection translates into a better outcome.

A second principle rests on the observation in this study that flucytosine works efficiently when combined with amphotericin B. Flucytosine remains one of the oldest antifungal agents in clinical use today, and yet, frequently, it still does not reach the patient. Cryptococcal meningitis is the leading cause of community-acquired meningitis in sub-Saharan Africa and is estimated to cause more than 600,000 deaths per year.[7] In fact, the mortality at 6 months among treated patients in Africa is at least 50% when combination therapy is not used,[8] yet this simple, off-patent nucleotide analogue is currently not available in most of Africa and Asia. Furthermore, in countries with advanced medical care, the fear of toxic effects frequently drives the interruption of flucytosine therapy. At my own medical center, a review of the duration of flucytosine induction therapy in 101 patients with cryptococcal meningitis showed that only 37% of patients received at least a 14-day course of this drug. These observations underscore the need for an increased effort on the part of all clinicians to administer flucytosine in combination therapy for at least 2 weeks for the treatment of cryptococcal meningitis.

Finally, the third principle embedded in this study is that the quantitation and monitoring of microbial load can matter and that measurements may be helpful. The management of infectious diseases has primarily focused on detection of the invading pathogen and its proper identification, but monitoring the host pathogen burden during treatment has not been a common strategy. Such a strategy was first used with the measurement of bacterial burden to predict a urinary tract infection and has recently been elevated to a clinical standard in the antiretroviral management of HIV infection with serial measurements of viral load. In this study and others,[6,9] we are starting to frame the question of whether we should start to calculate and use the early fungicidal activity in cryptococcal meningitis during the induction-treatment phase to properly understand the success of the treatment and provide us with guidance for optimizing it. These therapeutic issues remain important to consider, since even with the most advanced medical care, the mortality associated with cryptococcal meningitis remains approximately 15 to 25%.[10] With no new drugs on the immediate horizon for the treatment of cryptococcosis, we must optimize the use of currently available agents, and this study creates a strong beacon for us to follow going forward. As shown in the study by Day et al., long-term success in the treatment of cryptococcal meningitis depends on how well we kill yeasts with the initial treatment regimen.

Cryptococcosis is the most common invasive fungal infection in the world and one of the most deadly. Robust studies like this trial provide important insights for how to manage cryptococcal meningitis better, and it is our job to implement its initial therapeutic principles, such as the use of rapid fungicidal regimens, worldwide.

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From the Division of Infectious Diseases, Duke University Medical Center, Durham, NC.

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The Duel between Dual Antiplatelet Therapies

Richard A. Lange, M.D., and L. David Hillis, M.D.

Current guidelines for patients who are being considered for percutaneous coronary intervention (PCI) recommend dual antiplatelet therapy (aspirin and a platelet adenosine diphosphate [ADP]–receptor antagonist) to minimize periprocedural complications.[1] Clopidogrel is usually administered in patients with stable angina,[2] whereas patients with an acute coronary syndrome may benefit from a more potent ADP-receptor antagonist. In such patients, prasugrel[3] or ticagrelor[4] before PCI, as compared with clopidogrel, results in an absolute reduction in ischemic periprocedural complications of approximately 2 percentage points and a relative-risk reduction of 16 to 19%, albeit with an increased risk of bleeding. Unfortunately, because all these agents are administered only orally, their antiplatelet effect first becomes evident 1 or more hours after administration. Accordingly, they should be given before the patient's coronary anatomy is delineated if PCI is planned during the same procedure. In addition, the antiplatelet effect of these agents persists for days after discontinuation. If coronary-artery bypass grafting is indicated, surgery is not recommended until 5 to 7 days after they are discontinued.

Bhatt et al.[5] now report in the *Journal* that cangrelor, an intravenously administered ADP-receptor antagonist that acts rapidly and has quickly reversible effects, reduced the rate of periprocedural PCI complications, as compared with clopidogrel, in patients with an acute coronary syndrome or stable angina. Patients undergoing PCI who received cangrelor (an intravenous bolus and an infusion for 2 hours or the duration of the procedure, whichever was longer) followed by 600 mg of clopidogrel at the termination of the infusion were less likely to have a primary composite end-point event of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours than were those receiving a 300-mg or 600-mg loading dose of clopidogrel (4.7% vs. 5.9%; odds ratio, 0.78; $P=0.005$). With respect to the individual end points, periprocedural myocardial infarction and stent thrombosis within 2 hours after randomization occurred less often in patients who received cangrelor than in those who received the loading dose of clopidogrel; no difference was observed with respect to the other end points. Importantly, cangrelor did not cause increased bleeding. These results differ from those of two previous trials, which failed to show that cangrelor administered before PCI reduced the rate of a composite end point of death, myocardial infarction, or ischemia-driven revascularization at 48 hours, as compared with placebo[6] or clopidogrel.[7]

Where does cangrelor fit in the armamentarium of dual antiplatelet therapy? Unfortunately, the study by Bhatt et al. does not answer this question definitively. In the patients given cangrelor, a maximal antiplatelet effect was operative before and during PCI; this was not true in