Recent Controversy involving Resveratrol

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Resveratrol was originally isolated from the roots of hellebore plant in 1940, but it attracted wider attention in 1992, when its presence was discovered in wine and was suggested as the explanation for the cardioprotective effects of wine, particularly red wine. Red wine contains more Resveratrol than white wine because red wine is fermented with grapes with skins, whereas white wine is fermented after the skin has been removed from the grape. Since the early 1990s, resveratrol, a strong antioxidant, has been shown to have health benefits on multiple fronts, including cancer, inflammatory disease, cardiovascular, and even thought to affect longevity.

Epidemiology

Several epidemiological studies indicate that moderate consumption of red wine is associated with a lower incidence of dementia and Alzheimer’s Disease (AD). The first study, published in 1997, reported that moderate to mild wine consumption was associated with a low risk of AD. Later, a study of individuals aged 65 years and older confirmed that intake of wine, but not other alcoholic drinks, was associated with a low risk of dementia, including AD. Furthermore, a prospective analysis of risk factors for AD in the Canadian population determined that wine consumption was the most protective variable against AD by reducing the risk of AD by 50 percent.

Resveratrol and Alzheimer’s Disease

In the field of AD, recent work indicates that resveratrol reduces beta-amyloid accumulation in cell cultures. Resveratrol does not inhibit beta-amyloid production, since it has no effect on the beta-amyloid-producing enzymes beta- and gamma-secretases, but instead promotes the clearance of beta-amyloid from the brain.
Nearly 4,500 scientific articles have been published about functions and effects of Resveratrol in the body and various disease. This past month, the media reported that a researcher who worked on the effects of resveratrol on cardiovascular health and longevity had fabricated data in many of his research projects. This scientific misconduct occurred only in the lab of this one researcher, who had a modest reputation in his field. The data do not appear to have any major impact at all on the larger body of scientific research involving resveratrol and related areas. Importantly, none of the research involved resveratrol in AD.

The Alzheimer’s data comes from multiple, independent labs from around the world, and has been validated over the past 10 years. The data from the AD research has been so compelling, that a clinical trial has been funded by the NIH, after rigorous review. In addition, as with any and all clinical trials, the resveratrol in AD data has also been reviewed by the FDA. Scientific integrity represents the core of the research enterprise, and it is unfortunate that this has occurred with regards to Resveratrol. The field will move on, continuing to strive towards finding a cure for this Alzheimer’s Disease with the latest scientific advances.

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So often patients and families ask how and why Alzheimer’s Disease (AD) develops. As clinicians, we provide the best answers available based on the most current research. However, we also use analogies to help explain things more clearly. There are three common analogies that we use in clinic to explain the ideas of: 1. Symptomatic versus disease modifying treatments; 2. Prodromal AD versus AD dementia, and; 3. The idea that the most common forms of AD may be due to “underexcretion” rather than “overproduction” of beta-amyloid.

Symptomatic versus Disease-Modifying Treatments

1. Symptomatic treatments simply relieve symptoms associated with a disease. They do not affect the underlying cause of the disease, and therefore do not affect the duration of the illness. Examples of symptomatic treatments include cold remedies. If a patient suffers from the common cold, and its associated symptoms such as sneezing, coughing, runny nose, and sore throat, physicians will often prescribe medications to reduce these symptoms. The patient still has the cold, and the cold will run its course. The natural progression of the common cold is such that the body’s immune system usually clears the virus, and the patient recovers.

The medications currently FDA approved for AD, reduce the symptoms associated with AD, such as forgetfulness, confusion, and difficulty performing activities, but these medications do not affect the course of AD, which in time progresses to more severe deficits that do not respond to these medications. A disease-modifying drug affects the course of the disease, and makes its duration less, or even stops its progression. Antibiotics are a good example of disease modifying medications. They stop an infection in its tracks. In the field of AD, we are actively testing drugs that are thought to be disease modifying, as they target the underlying cause of the disease, toxic beta-amyloid.

Prodromal AD versus AD dementia

2. Another analogy is used to convey the idea that, decades before AD, dementia becomes apparent in a patient, there is an underlying pathological process that affects the brain. High cholesterol levels are associated with a higher incidence of heart attacks. However, a patient does not present to their doctor with any symptom associated with high cholesterol. In fact, until 25 years ago when cholesterol levels started to be routinely checked, many patients would present with a heart attack as the first symptom of their long standing high cholesterol levels. The same is thought to be true about
AD. The symptoms of dementia are to the brain much like a heart attack is to the heart. By the time the symptoms of dementia have developed, there have been years of an underlying pathological process affecting the brain, namely the accumulation of beta-amyloid and the loss of synapses and neurons. And, much the same way, if a patient goes to the emergency room with a heart attack, prescribing a cholesterol lowering medication for the first time may be too late. Specifically, 15 to 20 years too late. Now that we can check cholesterol levels earlier in life with a simple blood test, in the absence of any symptoms, we can start patients on cholesterol-lowering medications to reduce their risk of heart attack in the first place.

The same is believed to be true about treatment of AD dementia. By treating AD early, by lowering beta-amyloid levels, we may be able to prevent the dementia phase from developing. One of the biggest hurdles in the field has been how best to predict which individuals are on their way to developing AD dementia. So far, measuring spinal fluid levels of beta-amyloid seems to be one of the most accurate method. Other techniques being studied include amyloid PET scans, volumetric MRIs and cognitive testing.

Overproduction versus Underexcretion

3. Gout is a kind of arthritis that occurs when uric acid builds up in blood and causes joint inflammation. This may occur if: a), the body makes too much uric acid; or b), the body has a hard time getting rid of uric acid. The exact cause is unknown. Interestingly, not everyone with high uric acid levels in the blood has gout. The diagnosis is made when the disease becomes clinically apparent and the patient has symptoms, or by the visualization of the characteristic crystals in joint fluid. Underexcretion of uric acid by the kidney is the primary cause of 90 percent of gout cases, while overproduction is the cause in less than 10 percent of cases.

There are some parallels with AD. Although it has been known for the past 20 years that all of the inherited forms of AD (five percent of all cases) affect the processing of beta-amyloid in the brain, leading to its “overproduction,” it was not until last year that it was shown that the non-inherited forms of AD (95 percent of all cases) are due to “underexcretion” of beta-amyloid from the brain. That is, most cases of AD seem to be due to an impaired ability of the body to remove beta-amyloid from the brain and into the blood stream, where it is rapidly cleared by the liver. The longer beta-amyloid stays within the confines of the brain, the more damage it causes to synapses and neurons, and eventually deposits into plaques. It is believed that different forms of the protein ApoE (2, 3 and 4) appear to regulate the removal of beta-amyloid from the brain, and they do so with different efficiencies. It has also been shown that ApoE4 seems to be the slowest in removing beta-amyloid from the brain, which may be why it confers the most genetic risk for the late-onset form of AD.

ADCS Trials Enrolling...

**Nerve Growth Factor Study (NGF)**

The NGF is a Phase II clinical study of Ceregene’s CERE-110, a gene therapy product designed to deliver nerve growth factor (NGF) to the brain for the treatment of Alzheimer’s disease (AD) is currently underway. This study is a randomized, double-blind, placebo-controlled trial and employs gene therapy to deliver nerve growth factor (NGF) directly into the brain.

[http://adcs.org/Studies/NGF.aspx](http://adcs.org/Studies/NGF.aspx)

**ADNI II Study**

The goal of the Alzheimer’s Disease Neuroimaging Initiative Study is to learn how to stop the progression of mild cognitive impairment (MCI) and Alzheimer’s disease in future generations. Information from the study might, in the future, lead to new treatments

[http://adcs.org/Studies/ImagineADNI2.aspx](http://adcs.org/Studies/ImagineADNI2.aspx)