

Age-Related Macular Degeneration



Yesterday

- Age-Related Macular Degeneration (AMD) was an untreatable disease that caused central vision loss. It was a major cause of blindness and the leading cause of new cases of blindness in people over age 65.
- AMD made it difficult, if not impossible, to read, recognize faces, drive a car, or perform even simple tasks that require hand-eye coordination.
- AMD severely restricted mobility, forcing many otherwise healthy seniors to prematurely lose their independence and ultimately to be cared for in costly assisted living facilities.
- From a research perspective, AMD was a poorly understood disease and the quest for treatments seemed daunting.

Today

- With Baby Boomers poised to reach retirement age, AMD is increasingly being viewed as an oncoming epidemic that could affect millions of Americans.
- Thanks to considerable research investment by the National Institutes of Health (NIH), the underlying causes of AMD are becoming understood and several treatments have emerged.
- In 1991 the Macular Photocoagulation Study (<http://www.nei.nih.gov/neitrials/static/study60.asp>), a large scale clinical trial funded by the NIH, established the value of laser treatment for advanced AMD to stabilize the condition.
- In 2000, the Food and Drug Administration (FDA) approved the use of a photosensitive agent called Visudyne as another laser-based treatment to prevent progression of advanced AMD.
- NIH researchers conducted a large scale clinical study called the Age-Related Eye Disease Study (AREDS - <http://www.nei.nih.gov/amd/>) and found that a daily regimen of antioxidant vitamins and minerals delayed the onset of advanced AMD by 25 percent. Advanced AMD is the most sight-threatening stage of the disease.
- Based on published data, an estimated 8 million older-age Americans are at high risk to develop advanced AMD. Of these 8 million, 1.3 million would develop advanced AMD within 5 years. However, now with the AREDS treatment, 300,000 of these patients could avoid the severe vision loss associated with advanced AMD over a 5-year period.
- Abnormal blood vessel growth, also known as angiogenesis, is a hallmark of advanced AMD. These faulty blood vessels leak serum and blood, damaging the macula and causing catastrophic central vision loss. NIH-sponsored laboratory research has established that a protein known as vascular endothelial growth factor (VEGF) spurs the development of abnormal blood vessels.
- New treatments that block the action of VEGF have been developed and two of these drugs, Macugen and Lucentis, have been approved by the FDA for treatment of advanced AMD.
- Avastin, a drug that is chemically very similar to Lucentis but much less expensive, is being used off-label for patients who cannot afford the higher priced Lucentis. Although Avastin is thought to be effective in treating AMD, there is no clinical trial data to support its use. To address this issue, the NEI launched the Comparison of Age-Related Macular Degeneration Treatments Trial (<http://www.nei.nih.gov/catt/>) to assess the safety and effectiveness of Avastin and Lucentis.
- NIH researchers also discovered a second protein, pigment epithelial-derived factor (PEDF), which blocks VEGF to prevent blood vessel formation. Early stage clinical trials evaluating a gene therapy approach with PEDF have shown promise.
- NIH-supported researchers recently identified subtle alterations in two genes, complement factor B and H, which account for 75 percent of the risk of developing AMD. These factors function as part of the immune system and normally respond to pathogens to fight infection. Alterations in these genes may result in an inappropriate response of the immune system, causing chronic inflammation within the macula and surrounding tissues. Chronic inflammation is thought

to start a cascade of pathologic events that result in AMD.

- A large genome-wide association study identified three additional genes associated with AMD. Two of these genes are involved in cholesterol transport, suggesting a new biologic pathway to the development of AMD.
- Many Americans must live with vision loss from AMD. The NIH's low vision research program supports the development of low-vision aids and rehabilitation strategies to help patients maintain independence and mobility. Additionally, the National Eye Health Education Program (NEHEP) (<http://www.nei.nih.gov/nehep/>) operates a low vision public education program to increase awareness of low vision and its impact on the quality of life.

Tomorrow

The NIH is poised to make major discoveries in the diagnosis and treatment of age-related macular degeneration.

- The NIH has invested substantial resources to understand the biologic mechanisms that inhibit and promote angiogenesis, including the isolation and characterization of key molecules and receptors in the process, the development of treatments, and the pre-clinical and clinical efforts to translate these findings into effective therapies. This knowledge has resulted in a fundamentally new way of treating AMD and many other diseases where angiogenesis plays a role. Several next generation antiangiogenesis agents have been discovered and new and improved treatments will emerge.
- The discovery of genetic risk factors in AMD provides an opportunity to predict those who may develop the disease many years before the onset of vision loss.
- These gene discoveries will also allow researchers to understand the fundamental nature of AMD. Knowledge of the underlying role of the immune system and cholesterol transport in the disease presents the possibility of developing treatments that preempt AMD long before it has a chance to damage vision.
- NIH researchers are conducting the Age-Related Eye Disease Study 2 (AREDS 2), a large-scale clinical trial evaluating supplementation of two antioxidant

carotenoids, lutein and zeaxanthin, and two long chain polyunsaturated fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), to prevent the onset of advanced AMD. Previous NIH studies have found high concentrations of lutein, zeaxanthin and DHA in the macula. Moreover, several studies have found an inverse relationship between dietary intake of these compounds and AMD. AREDS2 is also evaluating these antioxidants in combination with the original AREDS antioxidant and mineral formulation. It is hoped that AREDS 2 results will offer a more effective treatment regimen to prevent the severe vision loss associated with advanced AMD.

- A highly novel drug and drug delivery method to prevent progression of AMD is being evaluated in clinical trials supported by the NIH. The treatment involves the use of cells that have been genetically engineered to produce ciliary neurotrophic factor (CNTF), a naturally occurring protein that has shown promise in animal models with retinal degenerative diseases. The cells are encapsulated in an implantable device that allows CNTF to diffuse into the retina. The drug delivery technology, known as Encapsulated Cell Technology, offers long-term administration of CNTF. Sustained drug delivery is essential in treating chronic eye diseases like AMD.
- NIH researchers have developed a high resolution imaging technology called optical coherence tomography (OCT) that allows clinicians to see fine cellular and tissue detail. This technology will be helpful in evaluating the response to treatments in clinical trials and more accurately diagnose AMD in its earliest stages.
- The NIH-sponsored National Eye Health Education Program (NEHEP) plans to create a new program to inform the public about the importance of early detection and timely treatment of age-related eye diseases, including AMD.

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