

Physician's Guide to  
**Amyloidosis**



**NORD**  
National Organization for Rare Disorders

*This booklet is dedicated to the memory of Dennis Krysmalski and Donald C. Brockman who contributed greatly to furthering understanding and awareness of amyloidosis.*



**Dennis Krysmalski**

October 26, 1946 – April 23, 2010

*Dennis Krysmalski was a beacon, guiding thousands of patients and families worldwide through the ordeal of amyloidosis. His dedication, energy and ready wit will be remembered by many, for he provided invaluable information and assistance to amyloid patients and their families. As a founder of the Amyloidosis Support Network, he pioneered and worked tirelessly to establish the first Internet-based patient support organization focused on amyloidosis.*



**Donald C. Brockman**

May 1, 1942 - July 2, 2004

*Donald Brockman was determined to find a way to support research for amyloidosis, and his determination in the face of the disease led to the formation of the Amyloidosis Research Foundation in 2003. With his intense competitive drive and cool scientific approach to problems, it was his hope and intention to support research into amyloidosis with the goal of finding cures. His vision led to the research grant program that has funded young investigators since 2005 and now, with the merger of the Amyloidosis Support Network and the Amyloidosis Research Foundation, is a key part of the work of the Amyloidosis Foundation.*

For information about NORD's programs and services, contact:

National Organization for Rare Disorders (NORD)

PO Box 1968

Danbury, CT 06813-1968

Phone: (203) 744-0100

Tollfree: (800) 999-NORD

Fax: (203) 798-2291

Website: [www.rarediseases.org](http://www.rarediseases.org)

Email: [orphan@rarediseases.org](mailto:orphan@rarediseases.org)

NORD's Rare Disease Database and Organizational Database may be accessed at [www.rarediseases.org](http://www.rarediseases.org).

Contents ©2010 National Organization for Rare Disorders®



*This booklet is the eighth in a series of free publications for physicians and other medical professionals. It is NORD's hope that patients and their families will benefit from this and other efforts to enhance awareness of the almost 7,000 rare diseases affecting an estimated 30 million Americans.*

## **What is amyloidosis?**

Amyloidosis is a systemic disorder characterized by the extracellular deposition of a protein-like material in multiple organs. The deposition of amyloid leads to progressive organ dysfunction. There are several types of amyloidosis, and they are classified according to their precursor protein.

The commonest types of amyloidosis and the organs the most commonly involved are shown in the table. Briefly, primary (*AL*) amyloidosis is a plasma cell dyscrasia closely related to multiple myeloma. *Familial amyloidosis* is usually inherited as an autosomal dominant disease. It is most commonly associated with a mutant transthyretin (TTR) molecule, which is inherently unstable, and which breaks down to produce amyloid. Rarer mutations of apolipoprotein A1 and A2, gelsolin, fibrinogen A $\alpha$ -chain and cystatin C may also cause familial amyloidosis. *Secondary (AA) amyloidosis* is derived from the inflammatory protein serum amyloid A, and occurs in patients with chronic inflammatory disease such as the rheumatic diseases, chronic inflammatory bowel disease, tuberculosis or empyema. *Senile amyloidosis*, in which the amyloid is derived from wild-type (normal) transthyretin, is a slowly progressive disease that affects the hearts of elderly men. Amyloid deposits may occasionally occur in isolation without evidence of a systemic disease; isolated bladder or tracheal amyloid are the most common such presentations.

## **Epidemiology**

It is estimated that there are between 1500 and 2500 new cases of AL amyloidosis annually in the United States. This is approximately 1/5 of the incidence of multiple myeloma and is similar incidence to that of Hodgkin's disease or chronic myelocytic leukemia. As the prognosis of untreated AL amyloidosis is poor, the prevalence (total number of cases) of each of the latter two diseases is higher than is AL. Familial and secondary amyloidosis is probably less common than AL amyloidosis, whereas senile amyloidosis is probably more common, but considerably underdiagnosed.

## **How does the disease present?**

Amyloidosis is usually a multisystem disease resulting in a wide spectrum of clinical presentations. Consequently, a patient may present to, or be referred to, one of several subspecialists, most commonly a nephrologist, cardiologist or neurologist. While an individual subspecialist may see few cases during his or her professional career, recent advances in therapy have rendered early and precise diagnosis critical if the patient is to fully benefit. Thus, a high degree of awareness on the part of primary care and specialist physicians is of great importance. The common presentations follow, but it is important to recognize that most patients have more than one organ involved and therefore the finding of a combination of any of the features below should heighten the suspicion of amyloidosis.

### **Kidney**

The kidney is the organ most commonly involved in AL and secondary amyloidosis, but it is rarely involved in the familial forms caused by transthyretin mutations. Proteinuria is the usual manifestation of renal involvement and is commonly heavy, resulting in the nephrotic syndrome. Less commonly, amyloid causes progressive azotemia as the initial manifestation of renal disease. Edema in the absence of heart failure is a feature of nephrotic syndrome, as is hypercholesterolemia that may be profound. Thus, new-onset edema or a sudden increase in, or unexpectedly high level of, serum cholesterol levels should be an indicator for the physician to test for proteinuria.

### **Heart**

Amyloid infiltration of the heart results in ventricular wall thickening and the development of heart failure. Rapidly progressive congestive heart failure with thick ventricular walls, without cavity dilation and with a relatively preserved ejection fraction,

is the classical presentation of AL cardiac amyloidosis. Because the cardiac muscle cells are damaged or destroyed, electrocardiographic voltage decreases. This leads to a paradoxical finding of thick left ventricular walls with low voltage, a combination that is very unusual in other heart diseases and which strongly suggests a cardiac infiltrative process. The heart is invariably involved in senile amyloidosis, often in TTR amyloidosis and almost never in the secondary amyloidosis.

## **Nervous system**

Although less common than renal or cardiac involvement, neuropathy may be a significant problem in amyloidosis. Occasionally, it is the presenting and predominant feature of AL amyloidosis and in specific mutations of familial amyloidosis (particularly Met 30, originally known as familial amyloid polyneuropathy), it is the primary feature of the disease. The neuropathy is often painless and sensorimotor in nature although neuropathic pain may be occasionally significant. In familial amyloidosis, the peripheral neuropathy is frequently accompanied by an autonomic neuropathy characterized by diarrhea, postural hypotension and, in the male, erectile dysfunction. Postural hypotension may be profound and result in recurrent syncopal episodes. Systemic amyloidosis does not involve the central nervous system.

## **Liver and gastrointestinal tract**

Some degree of hepatic involvement is common in AL amyloidosis. It is also common in AA amyloidosis but is not seen in transthyretin-related familial amyloidosis. In most cases, hepatic involvement is asymptomatic, despite hepatomegaly that may be profound. Generally, the amyloid-infiltrated liver feels very hard, and alkaline phosphatase is moderately or markedly elevated with normal or near-normal transaminases. Elevation of bilirubin is an ominous sign and may portend hepatic failure. Hepatic amyloidosis rarely occurs in isolation and is usually associated with organ involvement elsewhere.

Diarrhea in amyloidosis is most commonly related to autonomic dysfunction involving the bowel. Occasionally, amyloid deposits anywhere in the GI tract may result in gastrointestinal bleeding. Loss of taste, and a difficulty eating solid foods because of macroglossia, may contribute to weight loss, or weight loss may be a non-specific manifestation of the systemic disease. In patients with autonomic neuropathy, gastric emptying is impaired, resulting in a sensation of early satiety.

## Soft tissue and skin

The dermatologic manifestations of AL amyloid may strongly suggest the diagnosis, particularly when other organ involvement suggests a systemic disease. Dermatologic involvement is almost exclusively limited to AL amyloid and consists of soft tissue, skin and vascular abnormalities. Periorbital purpura is a result of capillary fragility and is virtually pathognomonic of AL amyloidosis. It may appear after coughing, sneezing, or straining for a bowel movement. Not infrequently, purpuric lesions may arise after such simple actions as rubbing the eyelids. Soft tissue infiltration may cause macroglossia and hoarseness, although examination of the vocal cords may appear normal.

## Pulmonary involvement

Amyloid deposits are commonly found in the lungs at autopsy of patients with AL or senile amyloidosis, but rarely cause any problems during life. Occasionally in AL, significant pulmonary infiltration may occur, resulting in a severe decrease in diffusing capacity. This almost invariably occurs in patients with co-existing significant cardiac involvement. Pleural effusions are quite common in patients with congestive heart failure due to amyloidosis, but large recurrent pleural effusions disproportionate to the degree of heart failure suggest pleural amyloidosis.

## Endocrine involvement

An elevation in TSH is very common in AL amyloidosis but overt hypothyroidism is rare. Adrenal infiltration is often seen at autopsy but frank adrenal failure is almost never seen.

## Diagnosis (see figure)

Tissue biopsy is the *sine qua non* of diagnosis. Amyloid deposits have a characteristic apple-green birefringence when stained with Congo red and viewed with a polarizing microscope. If the disease is suspected on clinical grounds, a biopsy of the involved organ will give the highest yield. Alternatively, staining of a subcutaneous abdominal fat pad aspirate frequently is positive in AL amyloidosis. Rectal biopsy as a diagnostic test for non-gastrointestinal amyloid is more invasive, and has a lower yield than fat pad aspiration and should not generally be used.

Once a tissue biopsy of amyloid has been established, it is mandatory to determine the type of amyloidosis. In AL amyloidosis, manifestations of a plasma cell dyscrasia

## Suggestive History and Physical Examination

Biopsy of abdominal fat or affected organ

Positive staining for amyloid\*

Immunofixation of serum and urine,  
Serum-free light chain assay  
Immunocytochemistry of bone marrow biopsy

Positive

**AL amyloidosis\*\***

Negative

Serum isoelectric focusing\*\*\*  
DNA analysis

Positive

**ATTR**

Negative

**Consider AA amyloidosis  
Non-TTR familial amyloidosis  
Senile amyloidosis**

\* Specialized stains for typing the amyloid are available, but are difficult to apply and should be performed only in centers skilled in the technique.

\*\* If the clinical picture is inconsistent with AL amyloidosis or if there is a suggestive family history, testing/staining for other types of amyloid should be pursued, as an unrelated monoclonal gammopathy may coincidentally be present.

\*\*\* Screening test for mutant TTR performed in a few specialized centers.

will be found 98% of the time. In 2% of cases, a B-cell lymphoma is identified as the cause of AL. Serum and urine protein electrophoresis are insensitive tests and often fail to demonstrate a paraprotein in AL amyloidosis. The more sensitive immunofixation and a serum free light chain assay should be performed. A bone marrow biopsy, with appropriate immunohistochemical staining, will demonstrate a clonal population of plasma cells in most cases.

If these tests are negative in the setting of a positive biopsy for amyloid, a type of amyloid other than AL should be suspected. Genetic testing of the transthyretin molecule can be performed. In the absence of mutations of transthyretin, very rare forms of familial amyloid may be present. However, if the patient is an elderly man with clinically isolated cardiac involvement, the most likely diagnosis is senile systemic amyloid (senile cardiac amyloid), a condition in which wild-type transthyretin is deposited in the heart. Specific immunostaining of appropriately preserved tissue is available at specialized centers and offers a high specificity for determining the type of amyloid. In particularly difficult diagnostic cases, mass spectrometry is able to determine precisely the molecular structure of the amyloid deposits.

## **Treatment**

The type of treatment available is driven by the type of amyloidosis and the clinical state of the patient. Chemotherapy forms the cornerstone of treatment for AL amyloidosis. Various regimens have been studied but the commonest include melphalan and dexamethasone given orally or high-dose melphalan given intravenously with autologous stem cell support. Both are equally effective but the use of oral melphalan on a monthly basis is associated with a higher risk of treatment-related leukemia. New agents active in multiple myeloma, such as bortezomib or lenalidomide, are also effective in AL and have been shown to provide a benefit in patients with relapsed disease. Further studies of these and other new agents is on-going. The most important determinants of long-term survival with AL are the presence of cardiac involvement and hematologic response to therapy.

Supportive therapy (treatment of congestive heart failure, attention to nutrition, treatment of autonomic neuropathy etc.) is a very important concomitant measure. Given the complexity of the disease, it is recommended that treatment be performed in the center with experience of amyloidosis, or at least that the patient should have an initial evaluation at such a center, with continued communication during treatment in the local community.

Familial TTR amyloidosis is treated, if possible, by removal of the source of the abnormal TTR production. Since the dominant source is the liver, liver transplantation is currently the treatment of choice in carefully selected patients whose disease is not too far advanced. In senile amyloidosis, therapy is supportive, but both for this disease and for ATTR, pharmacologic therapies aimed at stabilizing the transthyretin molecule and thus preventing amyloid formation are being actively investigated. Clinical testing of the non-stroidal agent diflunisal and of a new agent tafamidis, a transthyretin stabilizer, is on-going at this time.



The mainstay of secondary amyloidosis treatment is therapy of the underlying disease. Renal transplantation has been performed successfully for renal disease due to secondary amyloidosis. Eprodinate is a small molecule that inhibits the formation of amyloid fibrils, and which seems to have a modest clinical effect in patients with secondary amyloidosis.

## Resources

This resource section is designed to direct you to more information should you need it for yourself, the patient or the patient's family. The following services are available to help you.

### **Patient Advocacy Organizations:**

- AF – Amyloidosis Foundation, Inc. [www.amyloidosis.org](http://www.amyloidosis.org)  
This foundation has been established to increase education and awareness of amyloidosis within the community and to provide financial support to medical and scientific research. Email: [info@amyloidosis.org](mailto:info@amyloidosis.org)  
Tel: 1-877-AMYLOID or 248-922-9610
- ASG – Amyloidosis Support Groups Inc. [www.amyloidosisupport.com/](http://www.amyloidosisupport.com/)  
ASG oversees patient & family face-to-face and Internet based support services. Email: [muriel@amyloidosisupport.com](mailto:muriel@amyloidosisupport.com)  
Tel: Toll-free at 866-404-7539 or 630-350-7539

### **Amyloidosis Treatment Centers**

The following centers have amyloidosis practices where they diagnose and treat the disease, conduct research and perform clinical trials.

- Boston University Medical Center - Amyloid Treatment and Research Program  
[www.bu.edu/amyloid](http://www.bu.edu/amyloid)  
Tel: (617) 638-4317
- Brigham and Women's Hospital/Harvard Vanguard Cardiac Amyloidosis Program, Boston, MA. [www.brighamandwomens.org/cvcenter/amyloidosis](http://www.brighamandwomens.org/cvcenter/amyloidosis)  
Tel: 617 421 6094
- The Mayo Clinic – Rochester MN [www.mayoclinic.org/amyloidosis/index.html](http://www.mayoclinic.org/amyloidosis/index.html)  
Tel: (507) 284-2111

- Tufts Medical Center – Boston, MA  
Tel: (617)-636-6454  
rcomenzo@tuftsmedicalcenter.org
- Memorial Sloan Kettering – New York City  
Tel: (212) 639-8808

## **Other US physicians with specific clinical expertise in amyloidosis:**

### ***Familial Amyloidosis***

- Merrill Benson, MD. Amyloid Research Group, University of Indiana, Indianapolis, IN.  
<http://www.iupui.edu/~amyloid>  
Tel. (317) 278-3426

### ***Cardiac Amyloidosis*** (also see above).

- Rodney H. Falk, MD. Harvard Vanguard Medical Associates, Harvard Medical School, Brigham and Women's Hospital, Boston MA. [rfalk@partners.org](mailto:rfalk@partners.org)  
Tel. (617) 421-6094
- Mathew Maurer, MD. Columbia Presbyterian Hospital, New York, NY  
(212) 305-9808

### **International Amyloid Centers** (both have informative Web sites).

- Italian center for the Study and Cure of Systemic Amyloidosis (Pavia, Italy.)  
[www.amiloidosi.it](http://www.amiloidosi.it)
- National Amyloidosis Center, London, UK. [www.ucl.ac.uk/medicine/amyloidosis/nac/](http://www.ucl.ac.uk/medicine/amyloidosis/nac/)

## **Other Resources**

- NORD – National Organization for Rare Disorders  
[www.rarediseases.org](http://www.rarediseases.org)  
Tel: (203) 744-0100 or (800) 999-NORD
- Leukemia & Lymphoma Society  
[www.leukemia-lymphoma.org/hm\\_lls](http://www.leukemia-lymphoma.org/hm_lls)  
Tel: (914) 949-5213 or (800) 955-4572

## Selected review articles:

Palladini G and Merlini G. Current treatment of AL amyloidosis. *Haematologica* 2009; 94:1044-1048 *A succinct but excellent and overview of the treatment of light-chain (AL) amyloidosis*. Available free on website <http://www.haematologica.org/>

Benson M. The hereditary amyloidoses. *Best Practice and Research Clinical Rheumatology* 17: 909-927; 2003. *A comprehensive and well-illustrated review of the hereditary transthyretin and non-transthyretin amyloidoses, their clinical features and treatment*.

**Reprint request:** [mbenson@iupui.edu](mailto:mbenson@iupui.edu)

Falk RH and Dubrey SW. Amyloid Heart Disease. *Progress in Cardiovascular Diseases* 52: 347-361; 2010 *Detailed review of the diagnosis, management and treatment of all types of cardiac amyloidosis*. **Reprint request:** [rfalk@partners.org](mailto:rfalk@partners.org)

Comenzo RL. *How I Treat Amyloidosis*. *Blood* 2009;114:3147-57.

Palladini G., Merlini G.  
*Current Treatment of AL Amyloidosis*.  
*haematologica* 94(8);1044-1048;2009.

Dember L. Amyloidosis-associated Kidney Disease. *J. Am. Soc. Nephrol.* 17: 3458-3471; 2006. *A comprehensive overview of the different forms of kidney disease associated with amyloidosis and the different types of amyloid that affect the kidney*. **Reprint request:** [ldember@bu.edu](mailto:ldember@bu.edu)

**NORD gratefully acknowledges the assistance of the following physicians in the preparation of this publication:**



**Rodney H Falk, MD, FACC, FRCP**

Director, Brigham and Women's Hospital/Harvard Vanguard Cardiac Amyloidosis Program

Associate Clinical Professor of Medicine, Harvard Medical School



**Dr. Raymond Comenzo**  
Attending Physician,  
Departments of Medicine  
and Pathology and Clinical  
Laboratories

Director, Bloodbank and  
Neely Cell Therapy Center

## NORD Guides for Physicians #8

- #1 The Pediatrician's Guide to Tyrosinemia Type I
- #2 The Pediatrician's Guide to Ornithine Transcarbamylase Deficiency...and other Urea Cycle Disorders
- #3 The Physician's Guide to Primary Lateral Sclerosis
- #4 The Physician's Guide to Pompe Disease
- #5 The Physician's Guide to Multiple System Atrophy
- #6 The Physician's Guide to Hereditary Ataxia
- #7 The Physician's Guide to Giant Hypertrophic Gastritis and Menetrier's Disease
- #8 The Physician's Guide to Amyloidosis
- #9 The Physician's Guide to Medullary Thyroid Cancer
- #10 The Physician's Guide to Hereditary Angioedema (HAE)
- #11 The Physician's Guide to The Homocystinurias

These booklets are available free of charge. To obtain copies, call or write to NORD or download the text from [www.rarediseases.org](http://www.rarediseases.org)

*This booklet was made possible by charitable contributions from the Amyloidosis Foundation. The series is intended to increase awareness of rare diseases and available resources. For additional copies, contact NORD.*

For information on rare disorders and the voluntary health organizations that help people affected by them, visit NORD's Web site at [www.rarediseases.org](http://www.rarediseases.org) or call (800) 999-NORD or (203) 744-0100.

---

NORD helps patients and families affected by rare disorders by providing:

- Physician-reviewed information in understandable language
- Referrals to support groups and other sources of help
- Networking with other patients and families
- Medication assistance programs
- Grants and fellowships to encourage research on rare diseases
- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals

Contact NORD at:  
[orphan@rarediseases.org](mailto:orphan@rarediseases.org).

National Organization for Rare Disorders (NORD)  
PO Box 1968  
Danbury, CT 06813-1968  
Phone: (203) 744-0100  
Tollfree: (800) 999-NORD  
Fax: (203) 798-2291