

**NATIONAL AMYLOIDOSIS CENTRE**  
**Centre for Amyloidosis & Acute Phase Proteins**  
**Department of Medicine**  
**Hampstead Campus, University College London**  
**Royal Free Hospital**  
**Rowland Hill Street, London NW3 2PF**



---

<b>Director/Professor of Medicine</b>	<b>Professor Philip N Hawkins</b>	<b>Tel: +44 (0)20 7433 2815/2816</b>
<b>Head, Dept of Medicine</b>	<b>Professor Mark B Pepys</b>	
<b>Hon. Consultant Physician</b>	<b>Dr Julian Gillmore</b>	<b>Tel: +44 (0)20 7433 2726</b>
<b>Hon. Consultant Physician</b>	<b>Dr Helen Lachmann</b>	<b>Tel: +44 (0)20 7433 2804</b>
<b>Hon. Senior Research Fellow</b>	<b>Dr Ashu Wechalekar</b>	<b>Tel: +44 (0)20 7433 2823</b>
<b>Clinical Fellow</b>	<b>Dr Mark Offer</b>	<b>Tel: +44 (0)20 7433 2823</b>
<b>Nurse Manager (appts)</b>	<b>Mr Paul Spencer-Gittens</b>	<b>Tel: +44 (0)20 7433 2813/2325</b>
<b>Senior Nurse Practitioner</b>	<b>Ms Sheril Madhoo</b>	<b>Tel: +44 (0)20 7433 2814</b>
<b>Clinic Nurse</b>	<b>Ms Annie Hughes</b>	<b>Tel: +44 (0)20 7433 2813</b>
<b>Admin Officer</b>	<b>Mr Mathew Betts</b>	<b>Tel: +44 (0)20 7433 2812</b>
<b>Fax:</b>	<b>+ 44 (0)20 7433 2817</b>	
<b>E-mail:</b>	<b><a href="mailto:amyloidosis@medsch.ucl.ac.uk">amyloidosis@medsch.ucl.ac.uk</a></b>	
<b>Web:</b>	<b><a href="http://www.ucl.ac.uk/medicine/amyloidosis/">www.ucl.ac.uk/medicine/amyloidosis/</a></b>	

---

The NHS National Amyloidosis Centre is the only centre in the UK specialising in amyloidosis and is part of the University College London Centre for Amyloidosis and Acute Phase Proteins, one of the world's leading centres for amyloid research. The Centre has "state of the art" clinical and research facilities, and a team of highly qualified clinical, research and support staff.

We pioneered scintigraphic imaging (scanning) of amyloid as a quantitative diagnostic procedure and provide a comprehensive clinical service for patients with all types of acquired and hereditary systemic amyloidosis. The NHS National Amyloidosis Centre is funded by the Department of Health to provide a diagnostic and management advice service for the UK's national caseload of patients with amyloidosis and related disorders, and we have evaluated 3000 patients during the past 7 years. The clinical service includes:

- Detailed clinical assessment.
- Diagnosis, quantification and monitoring of amyloidosis with whole body SAP scintigraphy.
- Review of diagnostic biopsies and specialised immunohistochemistry to determine amyloid type.
- Characterisation and exclusion of hereditary amyloidosis by DNA testing; genetic counselling.
- Recommendations for treatment and monitoring response.
- Measurement and monitoring of specialised biochemical (blood) tests for serum free light chains and serum amyloid A protein.
- 6-12 monthly follow-up to assess response and further treatment requirements.
- Providing information and support to amyloidosis patients, their families and health providers.
- Systematic evaluation of existing and new treatments.
- Diagnosis, monitoring and treatment of inherited fever syndromes.

*Index key words: amyloidosis, amyloid, London, UK, diagnosis, treatment, DNA, hereditary, familial, familial Mediterranean fever, National Amyloidosis Centre, Hawkins PN, Pepys MB, Royal Free Hospital, UCL.*

## **Index**

Amyloidosis	3
Diagnostic Imaging of Amyloidosis: The SAP Scan	4
Effectiveness of Treatment for Amyloidosis	4
Clinical Services provided by the National Amyloidosis Centre	4
Overseas and non-NHS entitled patients	5
Future Developments and Research	5
Amyloidosis: Some General Information and Specific Questions	6
Management and treatment of Systemic AA Amyloidosis	9
Management and treatment of Systemic AL Amyloidosis	11
Management and treatment of Hereditary Amyloidosis	14
Inherited Fever Syndromes	16

## Amyloidosis

The term amyloidosis describes a group of disorders caused by abnormal folding, aggregation and accumulation of certain proteins in the tissues, in an abnormal form known as amyloid deposits. These deposits are composed of abnormal protein fibres, the so-called amyloid fibrils that accumulate more quickly than they are cleared away, and which progressively interfere with the structure and function of affected organs throughout the body. Normal healthy proteins are cleared away at about the same rate that they are produced, but proteins that have formed amyloid are broken down only very slowly.

About 23 different proteins have been found to form amyloid in man, but only a few are associated with clinically significant disease. Amyloidosis is classified according to the protein that forms the amyloid fibrils, and the clinical picture and symptoms can differ greatly between one amyloid type and another. The proteins that cause the two most common types of systemic amyloidosis (i.e. the types that can affect many parts of the body) are produced in the presence of other disorders. Patients with systemic AL amyloidosis (formerly known as primary amyloidosis) have an underlying bone marrow disorder, and patients with systemic AA amyloidosis (formerly known as secondary amyloidosis) have some form of long-standing inflammatory disorder. Other types of amyloidosis have a genetic basis, most of which can now be identified by DNA tests.

Amyloid deposits can accumulate virtually anywhere in the body or can remain localised to one particular organ or tissue. Symptoms occur as a result of progressive damage to affected organs and tissues, for example the kidneys or heart, and may vary greatly from patient to patient.

Although various specific anti-amyloid drugs are under development, none as yet has been introduced into routine clinical practice. However, available treatments for the various conditions that underlie amyloidosis can stabilise or improve organ function, and may greatly improve the outlook. Contrary to previous beliefs, we have shown that amyloid deposits often gradually diminish in patients whose underlying conditions respond to treatment.

Sometime truly localised forms of amyloidosis can cause significant disease, for example in the airways, skin or bladder, and patients on long-term dialysis may develop amyloid in the bones and joints. Localised amyloid deposits composed of a protein called A $\beta$  occur in the brains of patients with Alzheimer's disease, but it is not known whether they are the cause of the disease. Fortunately, the brain is almost never directly involved in systemic amyloidosis.

The National Amyloidosis Centre offers a clinical service for patients with all types of amyloidosis other than Alzheimer's disease, although its research programme does include the latter. There are three main types of systemic amyloidosis – AA, AL and hereditary - which are described in more detail below. Systemic AA amyloidosis occurs in up to 5% of patients with chronic inflammatory diseases, most commonly rheumatoid arthritis, and systemic AL amyloidosis occurs in a small proportion of patients who have either multiple myeloma (a bone marrow cancer) or, much more commonly, a non-malignant disorder of the bone marrow. Unfortunately, both AA and AL amyloidosis cause rather non-specific symptoms, and diagnosis is often delayed until many investigations, often culminating in a tissue biopsy, have been performed. Systemic AL amyloidosis is now 2 or 3 times more common than AA type in the UK, and together there are probably about 500-1000 new cases each year.

## **Diagnostic Imaging of Amyloidosis: The SAP Scan**

In 1987 we devised a completely new diagnostic test for systemic amyloidosis comprising a whole body scanning procedure called SAP scintigraphy. This scan can show the distribution and amount of amyloid within the body's organs without the need for biopsies. SAP scans take about 45 minutes and are performed 6 to 24 hours after an intravenous injection of a small dose of radioactive tracer. The procedure delivers a very small radiation dose similar to a routine X-ray. The scan is specific and is now used routinely as part of our clinical assessment. The procedure is safe and painless and can be repeated every 6 to 12 months to monitor the course of the amyloid deposits and therefore help guide the need for on-going treatment. We have performed over 5000 scans and have obtained a large amount of information that has greatly improved our understanding of amyloidosis and encouraged a much more vigorous approach to its treatment. In particular, we have shown that amyloid deposits often disperse when the underlying disease is controlled, and this is usually accompanied by an improvement in general health.

## **Effectiveness of Treatment for Amyloidosis**

Although relatively few formal clinical trials have been conducted due to the rarity and diversity of amyloidosis, the principles and objectives of treatment are now clear. Until drugs become available that can specifically target amyloid deposits, therapy is aimed at suppressing production of the amyloid forming protein, whilst supporting the function of damaged organs. This involves treating the underlying condition, such as rheumatoid arthritis or bone marrow abnormality, as rapidly and completely as possible. Treatment varies depending on the type of amyloid but this typically requires powerful anti-inflammatory drugs in AA and chemotherapy in AL amyloidosis, and a majority of patients do derive significant benefit. Liver transplantation can halt some forms of hereditary amyloidosis, and dialysis-related amyloidosis can be reversed following renal transplantation. The prognosis depends very much on the degree of response to treatment, which varies between patients.

## **Clinical Services provided by the National Amyloidosis Centre**

We provide a comprehensive diagnostic and consultation service for patients with systemic AA, systemic AL, hereditary systemic and localised amyloidosis (not including Alzheimer's disease). Our approach to each patient with amyloidosis is tailored individually to the type of amyloid and to patients' particular problems. Wherever possible, patients are discussed with the referring physician, after which we re-examine any available tissue biopsies. Clinical evaluation of patients can usually be completed over 1-2 days during which hospital or hotel accommodation can be arranged. Investigations include whole body SAP scanning to establish the distribution and quantity of amyloid throughout the body, blood and urine tests, a detailed echocardiogram (ultrasound scan of the heart), and specific additional tests that might include DNA analysis (on a blood sample), and a bone marrow examination under local anaesthetic.

Treatment is usually administered at patients' local hospitals or at other regional centres in conjunction with advice from and reviews at the National Amyloidosis Centre. A small proportion of cases are managed directly by ourselves and our colleagues at the Royal Free Hospital.

Most patients with amyloidosis need long-term surveillance, with six-monthly or annual specialist follow up in the shorter term. Follow up SAP scintigraphy is the only means of quantitatively monitoring the amyloid deposits, and this information helps determine ongoing requirements for treatment. A careful balance is required in each patient between administering sufficiently 'strong' treatment, and minimising adverse effects. Another important role of our unit is to provide patients and their families with counselling and information that may not be available elsewhere.

## **Overseas and non-NHS entitled patients**

The Royal Free Hospital and the National Amyloidosis Centre welcome overseas patients. European Union residents may be entitled to an NHS assessment in the UK under EU reciprocal arrangements for medical care that is not available locally (EU 112 form). Non-NHS entitled patients are welcome but are usually liable to charges.

## **Future Developments, research and clinical trials**

Teams throughout the world are carrying out research in order to further the understanding of amyloidosis. This research has already identified many helpful treatments, and will undoubtedly lead to discovery of new ones. We hope that specific anti-amyloid drugs will become available in the near future, but these will need to be tested on consenting patients in clinical trials before they can be used generally.

We are actively involved in developing and studying new drugs and studying novel methods of treating amyloid and improving the available supportive treatments. At any given time it is likely that the NAC will be conducting a variety of studies (clinical trials). If you are eligible to participate in a clinical trial, we will provide information during your consultation for you to be able to make an informed decision about taking part in the trial. Should you decide not to participate, this will have absolutely no impact on your clinical care.

## **Summary**

The National Amyloidosis Centre is the only centre in the UK dedicated to the needs of patients with amyloidosis. Treatment is now available for most types of amyloidosis, but accurate diagnosis and 'aggressive' intervention are essential. Treatment varies a great deal according to the precise type of amyloid and which organs are involved, but for many patients the treatment options include chemotherapy and, for a few, solid organ transplants. Follow-up SAP scans to measure the amyloid load and other tests that measure organ function and the response to treatment of the underlying amyloid-causing condition enable the disease to be monitored optimally. Regular and comprehensive assessments guide each patient's management and their ongoing requirement for treatment, as well as minimising toxic side-effects and providing support and information to patients and their families.

## **AMYLOIDOSIS: Some general information and specific questions**

### ***What is Amyloidosis?***

There are various types of amyloidosis, all caused by aggregation and accumulation of specific proteins in tissues and organs throughout the body. These proteins exist in an abnormal fibre-like form (amyloid fibrils, amyloid deposits) that build up and progressively interfere with the structure and function of affected organs throughout the body. Different proteins are implicated in different types of amyloid, and treatment depends on precise identification of the particular amyloid protein. Amyloidosis is a general name for the disease, and amyloid is the name of the abnormal protein deposits that accumulate in the body.

### ***How is Amyloid made?***

Most amyloid-forming proteins are present in the blood, some made in the liver (e.g. in AA amyloidosis) and others made in the bone marrow (AL amyloidosis). The process of amyloid formation can occur when these proteins are either being produced in excessive quantity (e.g. in AA amyloidosis) or in abnormal forms (e.g. in AL amyloidosis) for one reason or another. The handful of proteins that can form amyloid are able to adopt an abnormal structure that enables them to aggregate in a very stable manner and become lodged in the tissues. It is not known what triggers the initial formation of amyloid but once the process is underway, amyloid tends to build up more quickly than it can be broken down. As a result amyloidosis is usually a progressive disease unless production of the particular amyloid forming protein can be reduced by treatment of the underlying disorder.

### ***Why are the amyloid-forming proteins produced?***

This varies with the type of amyloid. The amyloid-forming protein in AA amyloidosis is called serum amyloid A protein (SAA); the concentration of SAA in the blood rises greatly in many inflammatory diseases, for example rheumatoid arthritis, and SAA is converted into AA amyloid in about 1-5% of patients who have persistently high levels. The amyloid-forming protein in AL amyloidosis is known as monoclonal immunoglobulin light chains, or often light chains for short; the abnormal light chain protein is produced by an abnormal line of 'clonal' plasma cells in the bone marrow, which do not usually cause symptoms in their own right. Patients with kidney failure can develop dialysis-related amyloidosis as a consequence of a blood protein called  $\beta_2$  microglobulin accumulating because it is normally cleared away by the kidneys. Hereditary types of amyloid occur when a gene is inherited from one or other parent that causes a blood protein to be made in a slightly abnormal form life-long. Inherited amyloidosis can usually be confirmed or excluded by DNA tests, though many individuals with potentially amyloid causing genes never actually develop the disease, and in those who do, it often progresses very slowly.

### ***What Types of Amyloidosis are there?***

There are actually over twenty different types of amyloid in man, many of which are extremely rare or do not cause significant disease. Some types of amyloid cause problems purely or mainly in just one part of the body. Among patients with systemic amyloidosis, i.e. amyloid deposits distributed to some extent throughout the body, AL type is most common, followed by AA type; hereditary amyloidosis accounts for about 10% of cases.

### ***How Does Amyloid Affect the Body and Cause Symptoms?***

The build-up of amyloid in various organs gradually interferes with their function. Amyloid commonly affects the kidneys and may cause them to leak healthy blood proteins into the urine (proteinuria or nephrotic syndrome), or to lose their ability to purify the blood effectively (renal failure). Amyloid in the intestine can cause poor appetite, diarrhoea or weight loss. Amyloid in the skin can cause easy bruising. Amyloid in the heart muscle causes it to become unusually stiff,

leading to fatigue, shortness of breath and fluid retention. Amyloid in the nerves can cause abnormal sensation and weakness, or interfere with the body's automatic functions such as bladder, bowel and blood pressure control. There is often some amyloid in blood vessel walls which can increase the risk of bleeding or bruising.

### ***What Symptoms does Amyloidosis cause?***

Symptoms are often very non-specific and include tiredness, weight loss, weakness and loss of appetite. More specific symptoms, related to particular organs, include swollen ankles (oedema) due to kidney or heart involvement, tingling in the fingers or toes (paraesthesiae) due to nerve involvement, or breathlessness due to amyloid in the heart.

### ***How is Amyloidosis Diagnosed?***

The diagnosis is often delayed because the signs and symptoms are not specific and vary greatly, so that the doctor has to think of the possibility of amyloidosis being present. The results of investigations vary tremendously from patient to patient, and although no blood test is diagnostic of amyloid, certain specialist blood tests can support the possible diagnosis. Ultimately the diagnosis is usually made when a tissue biopsy (small tissue sample) is obtained, processed and examined under the microscope. Biopsies can be taken from almost any organ, and are performed either because a particular organ is not functioning properly (for example, the kidneys), or because the possibility of amyloidosis has been considered. In the latter situation, a small biopsy may be taken from the rectum since the procedure is quick and safe, and the sample usually contains a few traces of amyloid. Biopsies are usually retained by hospitals in a preserved state for many years; we often find it valuable to re-examine them in our own laboratory and to perform additional specialised tests to try to determine the precise type of amyloid.

### ***What is an Amyloid Scan (SAP scan)?***

We have developed a whole body scan (known as SAP scan, SAP scintigraphy or amyloid scan) which is diagnostic in most cases and shows the location and quantity of amyloid deposits in organs throughout the body. SAP is a normal healthy blood protein that we have purified, and which we tag with a trace of radioactive iodine that can be imaged throughout the body by a gamma camera scanner. Most patients with systemic amyloidosis have at least some amyloid in sites other than that which may have been biopsied, even when such organs appear to be functioning normally. Unlike biopsies which can show microscopic traces of amyloid in a small sample, SAP scans provide a whole body overview, and, uniquely, can monitor changes in the amount of amyloid and response to treatment over months and years. Unfortunately hollow or moving organs such as the gut and heart cannot be assessed reliably by SAP scans, but it remains important to look for amyloid in other organs in patients with suspected or proven gut or heart amyloid. The development of SAP scans has dramatically reduced the need for biopsies in our unit and helps us to tailor individual treatment.

### ***Is the Amyloid Scan dangerous, how is it performed, and does it have side effects?***

There is no inherent reason why this test should produce adverse effects, and none have occurred in over 4000 patient studies. The dose of radioactivity is very small and is comparable with a routine X-ray. To put this into perspective, a patient living in London who has two SAP scans per year may receive less radiation than residents in some parts of south-west England, where background environmental levels of radiation are a little higher. The radiation dose is minimised by administering potassium iodide before the procedure, a natural mineral that reduces absorption of radiation. The SAP protein itself has been purified from healthy blood donors, and has been duly treated and tested to minimize any risk of contamination or infection etc. Radiolabelled SAP is given by intravenous injection 6-24 hours before images are obtained by a whole body gamma camera scanner. The scanner is an open device on which patients lie fully clothed for about 40 minutes whilst the images are produced. A technician, and if desired a carer, stay in the room

whilst the scan is performed. It is not necessary to avoid food, drinks or any medication beforehand.

### ***What Treatments are Available?***

Just 20 years ago amyloidosis was widely considered to be untreatable but there are now treatments for most types of the disease, and these can be very effective. The actual treatment varies for each type of amyloidosis, but the principles and objectives are similar. At present no drug is available that has a direct effect on amyloid deposits, and current treatments are aimed at reducing the amount of the particular amyloid forming protein in the bloodstream, by treating the underlying disorder. When ongoing amyloid deposition can be slowed or halted, the existing amyloid deposits often gradually regress. One way to think of it, is to imagine filling a basin that has only a tiny outlet; filling the basin with water represents production of amyloid, and the outlet represents the body's limited capacity to remove amyloid. If the tap is left to run, water builds up in the basin, despite some drainage. When the tap is turned down sufficiently, the water can slowly drain away.

No particular diet or life style has been shown to affect amyloidosis, although, curiously, mice with amyloidosis that are given vitamin C supplements seem to remain in better health. If patients wish to pursue this, we recommend a modest supplement of 250 mg daily. Very large doses of vitamin C may be harmful. Dietary, salt or fluid restrictions may be necessary due to heart or kidney problems in some patients.

The other important aspect of treatment is protection and support of the organs affected by amyloid. Organs that contain amyloid, particularly the kidneys, are much more vulnerable to stress, for example, caused by high blood pressure, dehydration, serious infections, general anaesthetics and surgery etc. Careful attention to these matters is critically important in a patient with amyloidosis, even when things are going well.

An outline of the principles of treatment for different types of amyloid is provided separately below.

### ***Is Treatment Effective?***

The aim of treatment is to suppress the underlying condition and therefore production of the respective amyloid forming protein in order to inhibit further amyloid deposition. So long as affected organs are not too badly damaged by amyloid, their function can stabilise and even improve. If new amyloid deposition is completely halted, up to 50% of the existing amyloid deposits can disperse each year, although the rate is much slower in some patients. Regression of amyloid is usually associated with improvement in general well being as well as stabilisation or recovery of organ function. Unfortunately organs that are severely damaged before treatment may continue to deteriorate despite new amyloid deposition having been completely stopped.

## MANAGEMENT OF SYSTEMIC AA AMYLOIDOSIS

AA amyloidosis used to be known as ‘secondary’ or ‘reactive’ systemic amyloidosis. This is because it occurs in patients who have some kind of long-standing inflammatory disorder. Examples include rheumatoid arthritis (adults and children), inflammatory bowel disease, tuberculosis, other chronic infections and familial Mediterranean fever. The list of inflammatory diseases that have occasionally given rise to AA amyloidosis is enormous and includes some very rare conditions, some of which do not necessarily cause symptoms in their own right. Although AA amyloidosis can never be hereditary as such, the underlying inflammatory diseases that predispose to it do sometimes run in families; a notable example of this is familial Mediterranean fever (FMF) – see separate information sheet below. The nature of the long-standing inflammatory disease is difficult to determine in a small proportion of patients who develop AA amyloidosis, some of whom are not even aware that they have had any such inflammatory disease at all.

Inflammatory diseases are accompanied by changes in the chemistry of the blood. The concentration of one particular blood protein called serum amyloid A protein (SAA) can increase from healthy levels of less than 3 mg per litre to more than 1000 mg per litre in the presence of inflammation, and it can remain elevated for as long as the inflammatory disease remains active. For unknown reasons, in a small proportion of such patients, SAA can at some point begin to be converted into AA amyloid fibrils, and become lodged in various tissues throughout the body. The average duration of inflammatory disease before AA amyloidosis occurs is around 20 years, but it can occur after just a few years in some cases. AA amyloid deposits tend to be greatest in the spleen, which does not usually cause any symptoms, and the kidneys where it most often does cause clinical problems. Damaged kidneys may lead to loss of healthy blood proteins in the urine and severe fluid retention (proteinuria and nephrotic syndrome), and can ultimately lead to complete kidney failure, requiring dialysis. AA amyloid can build up in the liver and gut at a later stage, though rarely in the heart.

### Treatment

Once the process of AA amyloid deposition has begun, as long as the underlying inflammatory disease remains active, excessive amounts of SAA continue to be produced and deposited as amyloid in the organs. The aim of treatment in AA amyloidosis is to control the underlying inflammatory disease and thereby reduce the amount of SAA in the blood. The lower the SAA concentration, the slower the rate of new amyloid deposition. If the level is maintained close to normal (i.e. less than 10 mg/l), there is at least a 50% chance that existing amyloid deposits will gradually regress, which maximises the chance of improvement in amyloidotic organ function. Even if the amyloid deposits merely stabilise, kidney function can improve. Persistent elevation of the SAA concentration is associated with a poor outcome in the long term.

Treatment depends on the nature of the underlying inflammatory disorder, as well as individual factors such as treatments already received. We measure levels of SAA in the blood monthly and can therefore determine whether the inflammation is adequately controlled. The SAA level is therefore a vital guide to treatment. Patients with AA amyloidosis who visit the National Amyloidosis Centre are provided with a kit for sending monthly blood samples to us by post. We typically perform the SAP amyloid scan annually to quantify the amyloid deposits. Serial scans will show how effectively a particular patient can clear away their amyloid deposits, and give an indication of the level of inflammation that is ‘safe’ in any particular case. We are pleased to send SAA results directly to patients to encourage their understanding and involvement in their own management.

The commonest inflammatory disease underlying AA amyloidosis is rheumatoid arthritis, for which there are now several new treatments that can be very effective in lowering SAA production. These include 'biological' treatments, which are protein drugs given by injection that can suppress the cycle of inflammation. Examples include anti-TNF drugs such as infliximab, etanercept and adalimumab. The vital aspect of clinical management, whatever treatment is pursued, is to demonstrate that it is effective in suppressing the inflammatory disease in terms of SAA concentration in the blood. Various different treatments may need to be tried before this can be achieved, and occasionally chemotherapy drugs in modest doses can be very effective in suppressing inflammation when more conventional drugs fail.

Some underlying inflammatory diseases have very specific and highly effective treatments, for example the drug colchicine in patients with familial Mediterranean fever, and the biologic drug anakinra in patients with Muckle-Wells syndrome. A few underlying inflammatory diseases can even be treated by surgery, for example Castleman's disease 'tumours'.

### **Outlook for patients with AA Amyloidosis**

Most patients with AA amyloidosis can now be treated with drugs that can slow down, stop or reverse the disease, and the outlook is often good. There are a large number of drugs which can be used to treat the underlying inflammatory diseases, and several new powerful anti-inflammatory treatments have recently been developed. Many of our patients have survived for decades since their AA amyloid was diagnosed. Kidney failure remains a serious problem for some patients, but even in these cases, kidney transplantation can restore excellent health. Perhaps surprisingly, it is rare for AA amyloid to significantly affect a transplanted kidney.

## **MANAGEMENT OF SYSTEMIC AL AMYLOIDOSIS**

AL amyloidosis used to be called 'primary systemic amyloidosis' and is now the most commonly diagnosed form of the disease. It is never hereditary. Patients with AL amyloidosis have an abnormal line of cells (called plasma or B cells) which are usually in the bone marrow, and which produce the amyloid forming protein. The AL amyloid forming protein is part of a protein called monoclonal immunoglobulin; the part that forms AL amyloid is called the light chain. Abnormal free light chains can be measured in the blood in about 95% of patients with AL amyloidosis. The underlying bone marrow disorder / monoclonal immunoglobulin producing disorder is known by many different names (plasma cell disorder, plasma cell dyscrasia, paraprotein disorder, monoclonal gammopathy, etc), and is very subtle in 80% of patients. This kind of subtle plasma cell abnormality is actually not uncommon in the general population, but it only leads to amyloidosis in about 2% of cases; in the absence of amyloidosis, it usually requires no treatment. The structure and properties of the abnormal light chain proteins are slightly different in every single patient with AL amyloidosis, accounting for the very different symptoms that may occur. In about 20% of patients with AL amyloidosis, the growth of abnormal plasma cells is more florid, and can be overtly cancerous - a condition known as myeloma. Myeloma cells gradually replace healthy bone marrow cells, leading to bone pain and infections. Full blown myeloma is a bone marrow cancer that needs chemotherapy treatment in its own right, whether or not the plasma cells are producing an amyloid forming protein. A patient with myeloma may develop (or present with) AL amyloidosis but it is rare for an AL amyloidosis patient (who does not have myeloma at presentation) to progress to full blown myeloma.

### **Symptoms**

AL amyloidosis occurs in about 1 in 1300 people, and the frequency increases with age. Most patients with AL amyloidosis are aged over 45 years, but it occasionally occurs in young adults. The amyloid deposits tend to be laid down in many parts of the body, although usually one or two organs are predominantly affected. AL amyloid can occur almost anywhere in the body except the brain and it can therefore cause a wide variety of symptoms, many which may be quite vague. Significant involvement of the heart, kidneys, liver, digestive system or nerves is not unusual and may cause a variety of serious problems attributable to these organs. Non-specific symptoms such as weight loss, easy bruising and general fatigue are also common.

### **Investigations**

Two days of tests at the National Amyloidosis Centre are typically required. These include the SAP scan, an echocardiogram, ECG, a series of tests on blood and urine samples and occasionally bone marrow examination. We do not usually repeat biopsies if they have already been performed, but we like to review the biopsy samples in our own laboratory. In some cases we perform DNA analysis to exclude hereditary amyloidosis, and if necessary we organise additional investigations e.g. to look at nerve or lung function. Perhaps surprisingly, in some cases it can still be difficult to prove that amyloidosis is of AL type, and diagnosis in these cases relies on thorough exclusion of AA and hereditary types. It is also important to appreciate that the underlying plasma cell disorder can occasionally be so subtle that it cannot be measured, which can make it more difficult to know when a patient has received sufficient chemotherapy. Conversely, the mere demonstration of a plasma cell / abnormal light chain disorder in a patient with amyloidosis does not prove that the amyloid is definitely of AL type.

### **Treatment**

Treatment is directed at the underlying bone marrow disorder. In principle, chemotherapy in patients with AL amyloidosis who have low grade plasma cell dyscrasias is the same as in those with myeloma. The aim of chemotherapy is to decrease the number of abnormal plasma cells

which will proportionately reduce production of the amyloid forming protein (i.e. light chain protein). Under these circumstances new amyloid formation will decrease, and existing amyloid deposits may gradually regress. Occasionally however, despite disappearance of the abnormal light chains after chemotherapy (i.e. an excellent clonal response), there may only be stabilisation of the amyloid deposits. Unfortunately regression of amyloid is slow and it often takes 6-12 months after the end of chemotherapy for patients to experience a significant improvement in health. Because of the serious nature of AL amyloidosis, it is desirable to suppress the bone marrow disorder as quickly and completely as possible. However, the treatment can be adjusted along the way according to response, adverse effects and personal preferences. The three month point is generally an important landmark to assess the light chain response to most intermediate dose chemotherapy regimens to decide whether to continue the same regimen, stop chemotherapy altogether or change to another regimen.

Chemotherapy for AL amyloidosis can be broadly divided up as follows:

**Low Dose:** Low dose tablet chemotherapy - usually melphalan with or without prednisolone (steroids). This is normally taken for 5-7 days each month, in cycles that are repeated every 4-6 weeks. This type of chemotherapy may need to be continued for up to 18 months.

**Intermediate Dose:** Combination chemotherapy - several drugs given together over 1-4 days, usually for up to 6 courses, 3-4 weeks apart. Commonly used drug combinations include the so called 'CTD' (cyclophosphamide, thalidomide and dexamethasone) protocol, and melphalan (either orally or intravenously) with or without dexamethasone protocol.

**High Dose:** High dose intravenous chemotherapy, usually a high dose of intravenous melphalan, requiring 'stem-cell rescue' - a single treatment lasting about one month. This might be the only treatment required, but it can, if necessary, be augmented by additional intravenous or low dose chemotherapy. This procedure is commonly referred to as autografting or autologous stem cell transplantation; the stem cells are collected from the patient prior to the high dose chemotherapy, and returned to the patient after chemotherapy in order to form a new bone marrow.

In myeloma (with or without amyloidosis in addition), the plasma cells are cancerous, and it is common practice to recommend 3-4 courses of intermediate chemotherapy to reduce the abnormal cells in the bone marrow followed by an autologous stem cell transplant.

Each regime has its own merits and disadvantages:

**Low dose** is relatively safe, but has a quite slow effect. It is often necessary to continue this type of treatment for 18 months, and it is very successful in only about 20-30% of cases. These tablets can make some patients feel quite unwell and fatigued, and tend to gradually deplete bone marrow reserves, which may exclude subsequent stem cell transplantation. Unfortunately, prolonged use of this type of treatment can lead to irreversible bone marrow damage in up to 20% of patients in the long term.

**Intermediate dose** acts more rapidly but has more short-term toxicity. Each 'cycle' of treatment carries up to 1-2% risk of death due to toxicity (i.e. up to 5-10% for a complete course). If side effects are severe, patients can step down to low dose treatments, or continue a more gentle form of intermediate dose chemotherapy. Most patients will receive between 4 and 6 monthly cycles of chemotherapy. The treatment may be oral or intravenous. Patients may lose hair and are likely to feel very fatigued during chemotherapy. Blood transfusions may be required and patients have an increased risk of infection during treatment. Patients over the age of 65-70 years are more liable to serious complications. Depending on the type of drugs used, bone marrow reserve can be preserved

so that further treatment, if necessary, is usually possible. Beneficial effects are seen in some patients within 6 months of starting treatment. This type of treatment is successful in nearly 50% of patients.

**High dose** involves a single very high dose of chemotherapy after which 'bone marrow stem cells', previously purified from the patient's own blood, are given back as a transfusion. The principle of this treatment is that the bone marrow is largely destroyed by the chemotherapy, and then the purified stem cells lodge in the bone marrow space and generate a new and hopefully healthy marrow from scratch. The marrow takes 2 or 3 weeks to regenerate and start producing all of the different types of blood cells. This procedure, often called stem cell transplantation, usually requires a 3-4 week hospital stay, mostly in semi-isolation to prevent infections. It carries a significant risk to the patient's life and is best suited to younger patients (usually those less than 60 years) and those who do not have serious amyloid disease in several different organs. Advantages are that the whole treatment is completed in just a few weeks and that it can result in improved health more quickly than other types of chemotherapy. About two-thirds of patients benefit substantially from this type of treatment, and some patients are much improved within 3-6 months. The chief drawback is the risk of serious adverse effects and even death in about 10 to 30% of those with amyloidosis, but the risk is lower in certain groups of patients.

Intermediate and high dose chemotherapy are inevitably associated with at least some nausea, poor appetite and tiredness. Temporary hair loss may occur. Vomiting during the chemotherapy can now largely be prevented.

This outline is meant to serve as a guide to the principles of treatment, but every patient with AL amyloidosis differs in many ways. The most suitable treatment regime for a particular individual depends on many factors including age, quantity of amyloid and which organs are affected. Treatment must therefore be tailored to each specific case. Occasionally, chemotherapy is not recommended. This can be the case in patients with mild or non-progressive amyloidosis, or in a very small proportion of patients who are sadly too ill to benefit from chemotherapy. Ultimately however, the decision to proceed with chemotherapy, and the type given, will be guided by each patient's wishes. Recruitment of newly diagnosed patients with AL amyloidosis into a clinical trial comparing various chemotherapy regimes is expected to begin in 2007. This trial will be run by members of the NAC but will be UK wide.

### **Does the Treatment Work?**

AL amyloidosis is usually a very serious condition, which, if left untreated, is progressive and typically fatal within 5 years. Chemotherapy for AL amyloidosis is beneficial in a considerable proportion of cases. Successful treatment inhibits progression of the disease and can result in regression of existing amyloid deposits. Whatever the type of chemotherapy, it is important to appreciate that improvement in amyloid related symptoms is often slow, and may not be apparent for 12-18 months. The success rate varies between treatments but is about 40% to 60% on average. In addition to chemotherapy, or in some cases, instead of chemotherapy, there are many other supportive measures that can help to reduce symptoms, maintain general wellbeing and assist the function of affected organs.

Overall, approximately 20-30% of patients can expect to derive considerable benefit from low-dose chemotherapy, after they have taken it for one year. Although stem-cell transplantation has not been available for long, the results so far suggest that more than 50% of patients respond very favourably within 6-12 months. The results of intermediate dose chemotherapy lie in between the other two, but are thought to be closer to those of stem cell transplantation. Long term monitoring for recurrence is required in all patients, though further treatment can be successful.



## **MANAGEMENT OF HEREDITARY AMYLOIDOSIS**

Hereditary amyloidosis is less common than AL or AA types. It is due to the inheritance of an abnormal gene (a 'mutation') which leads to life-long production of a potentially amyloid forming protein. Most familial forms of amyloid do not cause any symptoms until middle age or later. They are all inherited in an autosomal dominant fashion. This means that if any particular individual has the condition, each one of their children has a one in two chance of inheriting the mutation, and that each of their brothers or sisters also has a 50% of having the abnormal gene. In contrast, individuals who do not have the abnormal gene themselves **cannot** pass the condition on to their children. Not all individuals who inherit one of these mutations will actually develop clinical problems. Some individuals develop only a small and insignificant amount of amyloid in their body, and others seem to accumulate none at all. This genetic phenomenon is called incomplete penetrance, and explains why some patients with hereditary amyloidosis do not have any family history of similar disease. Penetrance varies markedly among different families, and information about a particular family is very important for estimating the likelihood that a young healthy individual with a mutation will eventually develop the disease.

### **Genetic testing**

We can analyse the genes that are associated with all known forms of hereditary amyloidosis. These DNA studies are usually performed on a simple blood sample that will be coded and tested anonymously. It usually takes about 4 weeks to obtain the full results. Individuals who are presently healthy, but are at-risk of having inherited a potentially amyloid causing mutation, may choose to undergo such DNA tests, but only after counselling with a physician from the National Amyloidosis Centre. Direct access to this service is available in our unit, and telephone enquiries are welcomed.

Different amyloid-causing mutations can cause completely different clinical features. The commoner ones are described below.

### **Familial Amyloid Polyneuropathy (FAP)**

This is by far the most common type of hereditary amyloidosis in the world. It is characterised by deposition of amyloid in nerves, causing limb weakness, loss of sensation, nerve pain, bowel, bladder and blood pressure disturbances and sexual dysfunction. The heart, kidneys and sometimes other organs can also be affected. FAP is progressive and can result in severe wasting, immobility and death within 5-15 years after symptoms first develop. It is due to mutations in a protein called transthyretin (or TTR). More than 80 amyloid forming variants of TTR are known of which the most frequent is called TTR Met30. FAP is common in some parts of Portugal, Sweden and Japan, but occurs throughout the world in very small numbers. Another mutation, TTR Ala60, occurs in the Irish population, and typically causes symptoms of heart failure after age 60 years.

### **Other forms of hereditary amyloidosis**

The other types of hereditary systemic amyloidosis are rare, and by and large do not cause nerve damage. In general, they present with high blood pressure and kidney disease in middle-age. The liver or heart can sometimes be affected.

### **Hereditary Fibrinogen A alpha chain amyloidosis**

A number of mutations in the fibrinogen A alpha chain gene are known to cause amyloid. The most common fibrinogen A alpha chain variant, Val526, generally presents with kidney disease after the age of 50, leading to complete kidney failure within a few years. Recent research suggests that many individuals with this particular mutation never get clinical disease. This type of amyloid can recur in kidney transplants within 7-10 years, and as in FAP the amyloid forming protein is

produced only in the liver, it is theoretically possible to completely halt the disease by liver transplantation. Studies are ongoing to compare the relative merits of combined liver and kidney transplantation versus kidney transplantation alone among patients with end-stage kidney disease due to hereditary fibrinogen A alpha chain amyloidosis.

### **Hereditary Apolipoprotein AI amyloidosis**

Several mutations in the gene for apolipoprotein AI cause amyloidosis. Patients with this form of hereditary amyloidosis usually present with high blood pressure and kidney disease in middle age. The amyloid often builds up in organs other than the kidneys including the liver and occasionally the nerves. Despite this, kidney failure is usually the most serious consequence of this type of amyloidosis. A number of patients have undergone kidney transplantation with excellent long-term outcome. Liver transplantation may be required in patients with severe amyloid damage to the liver, or sometimes as a means to reduce or halt progress of the disease in other organs (as in FAP and hereditary fibrinogen A alpha chain amyloidosis above).

### **Hereditary Lyzosome amyloidosis**

This is one of the rarest types of hereditary systemic amyloidosis, and has only been found so far in a few families. Like hereditary apolipoprotein AI amyloidosis, it usually presents with kidney problems but there can be extensive amyloid in other organs, especially the stomach lining. This form of amyloid tends to build up very slowly indeed and can remain stable for many years.

### **Treatment**

The principles of treatment for hereditary amyloidosis are the same as for other types of amyloidosis. Whilst there is, as yet, no treatment that blocks amyloid deposition or speeds up its removal, treatment is aimed at supporting the function of failing organs and, in some instances, reducing production of the genetically abnormal amyloid forming protein by liver transplantation. Kidney failure often dominates the clinical picture and a kidney transplant may effectively restore normal health for a long time.

Liver transplantation as a treatment for hereditary amyloidosis has been used most extensively so far in patients with familial amyloid polyneuropathy (FAP), in whom the abnormal amyloid-forming protein, called transthyretin (TTR), is made almost exclusively in the liver. Replacement of the liver by a liver that makes normal transthyretin protein is aimed at preventing the formation of further amyloid and can stabilise the disease. Liver transplantation has now been performed in hundreds of patients with FAP worldwide, with great success in many cases. As experience increases it is becoming clear that liver transplantation for FAP should take place before too much damage to the nerves or heart has already occurred. Sadly, the latter may occur without causing any symptoms.

### **Outlook for patients with hereditary amyloidosis**

The outlook for patients with hereditary amyloidosis depends on the protein type, the specific genetic defect and on the particular characteristics of the disease in a given patient, all of which are extremely variable. The recent development of liver transplantation for FAP, the commonest type of hereditary amyloidosis, offers a method to halt the disease for some patients with this particular form of the disease. In general, the prognosis of hereditary amyloidosis is much better than for systemic AL amyloidosis, though there are implications for family members, for whom we can provide genetic counselling and DNA testing.

## **THE INHERITED FEVER SYNDROMES**

These are a group of genetic diseases which usually present in childhood with fever often accompanied by rash and pain. Although these diseases are not new they are rare and have only been properly described and named in the last few decades. Since 1997 four separate genes have been found to be responsible for the different syndromes. We still do not fully understand why mutations in these genes cause fevers but there is a lot of ongoing work to understand this and to develop new treatments. The four inherited fever syndromes (also called autoinflammatory diseases) for which we can offer specific diagnostic testing are summarised briefly below. Without effective treatment, a proportion of patients with inherited fever syndromes develop AA amyloidosis.

### **Familial Mediterranean fever (FMF)**

FMF is the commonest inherited fever syndrome. Although the prevalence is higher among people of Mediterranean ancestry it can occur in almost any ethnic group. In most cases the first attack of FMF occurs in childhood. Attacks usually last 3 days and consist of a high fever and severe pain in the abdomen or less frequently the chest. The pain may be so severe that the first attack is thought to be appendicitis. Between attacks, affected individuals feel entirely well and grow and develop normally.

FMF is due to the inheritance of two abnormal copies of a gene, one from each parent, described as autosomal recessive inheritance. This means that if both parents carry the abnormal gene, each child has a one in four chance of inheriting the condition. Brothers or sisters of an affected individual also have a 25% chance of having two mutations and developing FMF, and a 50% chance of carrying one abnormal copy of the gene (a carrier). FMF carriers very rarely develop symptoms and are very unlikely to have an affected child if their partner is not a carrier. FMF is now known to be caused by mutations in the *MEFV* gene which encodes a white blood cell protein called pyrin. The mechanism whereby abnormal pyrin causes fever is not fully understood. It is thought that pyrin may make white blood cells 'overactive' so that attacks of inflammation occur spontaneously.

The treatment for FMF is a drug called colchicine which is effective at preventing attacks in the vast majority of patients, so long as sufficient doses are taken. Colchicine has been very widely used and more than 30 years experience in FMF has shown it to be very safe at the usual doses of 0.5 to 2mg per day. Colchicine is also effective in preventing development of AA amyloidosis in most patients with FMF.

### **TNF receptor associated periodic syndrome (TRAPS)**

TRAPS is the second commonest of the inherited fever syndromes. It is inherited in a dominant fashion - this means that if any particular individual has the condition, each one of their children has a one in two chance of inheriting the mutation, and that each of their brothers or sisters also has a 50% of having the abnormal gene. In contrast, individuals who do not have the abnormal gene themselves cannot pass the condition on to their children. Not everybody who inherits an abnormal gene actually develops clinical problems so there may be no family history.

The symptoms in TRAPS can be very variable and can mimic FMF and HIDS (see below). In general, attacks start in childhood; fevers last around 10 days or more and can be accompanied by abdominal pain, rash, muscle pains and swelling. Diagnosis rests on suspicious symptoms and the finding of a mutation in the *TNFRSF1A* gene. This is the gene which encodes a protein receptor for tumour necrosis factor alpha. The exact mechanisms by which abnormal TNF $\alpha$  receptors cause spontaneous attacks of inflammation and fever are not fully understood.

Colchicine is not usually effective in TRAPS. Steroid therapy can be beneficial during attacks and TNF $\alpha$  blocking drugs (which are widely used in rheumatoid arthritis) can also be effective.

### **Hyper immunoglobulin D syndrome and periodic fever syndrome (HIDS)**

Like FMF, HIDS is a recessively inherited condition. It is extremely rare and mostly occurs in populations from North Western Europe. Affected children usually develop recurrent attacks of fever in their first year of life, each typically lasting 3 to 7 days. These are often accompanied by headache, enlarged lymph nodes (glands) in the neck, joint pains, diarrhoea, vomiting and rash. Attacks classically occur within hours of immunizations or minor infections and the disease usually gets better in adolescence.

This syndrome is due to mutations in the *MVK* gene which encodes an enzyme called mevalonate kinase. Treatment of HIDS involves avoiding immunizations as these are well known to precipitate attacks. Drug treatment is difficult although there is now evidence that agents which block certain inflammatory proteins (cytokines) such as TNF and IL-1 may be effective.

### **Muckle Wells Syndrome (MWS), Familial Cold Urticaria (FCU) and Chronic Infantile Neurological Cutaneous and Articular Syndrome (CINCA) (also known in USA as Neonatal Onset Multisystem Inflammatory Disease, NOMID)**

These three diseases are part of a single spectrum. FCU is the mildest and causes attacks of itchy rash, red eyes and fever within hours of exposure to cold. Most affected patients come from North America. MWS is the type most often seen in the UK. It causes daily episodes of generalised rash, red eyes and fever. These usually present soon after birth and are worst in the evenings. About a quarter of patients will become deaf later in childhood. CINCA (NOMID) is the most severe and causes chronic inflammation of the lining of the brain resulting in loss of hearing, poor vision and developmental delay. Children with CINCA can also have problems with their bone growth, and typically develop the rash and fever seen in the other two conditions.

MWS and FCU are dominant diseases although as with the other fever syndromes some patients will have no affected relatives. Although CINCA is due to mutations in the same gene, these usually develop for the first time in the affected individual and so other family members are usually not affected. The gene responsible for these conditions is known as *NALP3* or *CIAS1*. It encodes a protein known as NALP3 or cryopyrin which is involved in controlling inflammation. As in the other fever syndromes the mutations which cause FCU/MWS and CINCA (NOMID) result in overproduction of inflammatory proteins. Until recently there was no treatment for these conditions; however, recent preliminary studies have shown IL-1 blocking drugs to be highly effective and we are currently recruiting for ongoing trials with these agents.