

child with a beating heart and spontaneous intact respiration, exceed 80% of those cases who arrive alive in the intensive care unit. All the studies of childhood freshwater pond and pool immersions have found a minimum of a 50% survival rate, and although better resuscitation is condemned by some as only 'secondary prevention', it offers a potential short term solution to saving many children's lives.

The biggest challenge to clinical management therefore is improving prehospital resuscitation. Questions about the efficacy of out of hospital resuscitation are controversial and topical,<sup>26 27</sup> but our experience with child near drowning victims leads us to the uncompromising viewpoint that 'every parent should be a first aider'. Attempts to institute such a policy, at least for pool owning families, have so far failed. However, by continued societal advocacy, paediatricians can create a public ambience where such must come to be regarded as one of the essential skills of parenting. May that time roll on.

### Prevention and a medical model

The biggest impediment to the solution of childhood immersions is the failure of the medical profession to adopt a medical model to deal with the problem. Despite the fact that immersion continues to rank as one of the major killers of young children in many parts of the world, many remain reluctant to accept this as a medical or public health problem. The techniques of preventive medicine are well honed in the area of infectious and nutritional disease as these occur in the childhood years. Genetic diseases are currently vigorously approached by the portals of genetic counselling and prenatal diagnosis. Child trauma more generally has responded to aggressive intervention using the traditional themes of preventive medicine, but drowning remains the poor relation when judged by any audit of results revealed in contemporary surveys. One reason for this is the very high fatality: survivor ratios for immersion accidents. For every child who drowns, another (1:1) is pulled from the water pulseless but who subsequently responds to resuscitation. In the case of road trauma the ratio is 1:20 and 1:2000 in the case of accidental poison ingestion. Thus the size of the problem is partly masked as most of the immersion victims bypass the hospital and go straight to the mortuary, and are not seen in the ambience of the intensive care wards. Furthermore, in many countries society at large has been conditioned by newspaper reports of yet 'another toddler drowning fatality'. It is thus by continued advocacy, and the use of traditional methods that have conquered other high ranking problems in preventive medicine, that this problem will be effectively addressed.

## Reactive amyloidosis

Reactive amyloidosis (also known as systemic amyloidosis or secondary amyloidosis) is a disorder which occurs as a complication of chronic inflammatory disorders such as juvenile chronic arthritis, chronic infective disorders such as bronchiectasis, osteomyelitis, tuberculosis, or leprosy in susceptible individuals. It is also responsible for renal failure in the hereditary form of amyloidosis associated with familial Mediterranean fever, particularly in North African Sephardic Jews.<sup>1</sup> Recently it has been described to have been the cause of the severe and rapidly fatal nephropathy which occurs in adolescents with cystic fibrosis.<sup>2</sup> The table is a summary of the different types of amyloidosis.

Fibrillar proteins are deposited together with glycos-

Currently the urgency of childhood immersions is the responsibility of us all.

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aminoglycans (GAG), serum amyloid P component, and fibrinectin, leading to cellular dysfunction. The spleen appears always to be involved in reactive amyloidosis. The kidneys, liver, adrenal gland, and gastrointestinal tract are frequently involved. By light microscopy, the amyloid deposit appears as a homogeneous eosinophilic material that stains with Congo red. Under polarised light microscopy the congophilic material has a characteristic apple green birefringence.

### Pathogenesis of reactive amyloidosis

The protein that forms the fibrils in amyloid deposits is

## Amyloidosis syndromes

Distribution of deposits	Clinical type	Chemical type	Fibril proteins and precursors
Systemic amyloidosis	Associated with immunocyte dyscrasia	AL	$\gamma$ or $\kappa$ light chains derived from monoclonal immunoglobulin light chains
	Associated with chronic inflammatory diseases	AA	Amyloid A derived from serum amyloid A protein
	Associated with chronic haemodialysis	AH	$\beta_2$ -Microglobulin
	Senile systemic amyloidosis	ASc	Prealbumin-like, derived from plasma prealbumin
	Hereditary syndromes:		
	Predominantly neuropathic forms (all autosomal dominant): Types I-IV	AFp	Mainly prealbumin variants
	Predominantly nephropathic forms: Associated with familial fever (autosomal recessive)	AA	Amyloid A derived from serum amyloid A
	Ostertage type (autosomal dominant)		Not known
	Muckle-Wells type (nephropathy with deafness, urticaria, limb pain)		Not known
	Predominantly cardiomyopathic forms:	AFc	Prealbumin variants
	Senile amyloidosis (heart, joints, seminal vesicles)		Atrial, natriuretic, peptide related fibrils in isolated atrial amyloid
	Localised amyloidosis	Cerebral amyloid angiopathy and cortical plaques in Alzheimer's disease, senile dementia and Down's syndrome	
Endocrine amyloidosis: Medullary carcinoma of thyroid insulinoma and type II diabetes		AE AEt	Prealbumin-like protein calcitonin related, peptide like protein in pancreas
Isolated massive nodular deposits (skin, lung, urogenital tract)		AL	Monoclonal immunoglobulin light chains
Primary localised cutaneous amyloid (macular, papular)			? Keratin derived
Ocular deposits (corneal, conjunctival)			Not known
Hereditary syndromes:			
Hereditary cerebral haemorrhage with amyloidosis (Icelandic type)		AFb	Cystatin C ( $\gamma$ trace), Glu58 genetic variant of cystatin C $\beta$ -protein
(Dutch type)			

derived from a serum acute phase protein, serum amyloid A. The carboxy terminal end of serum amyloid A is cleaved off leaving the first 76 amino acids, which then form polymers resulting in  $\beta$ -pleated sheets of fibrils embedded in GAG, serum amyloid P, and possibly other extracellular matrix proteins. The local appearance of GAG appears to be coincident with the time that the fibrillar proteins are deposited in experimentally induced amyloidosis in mice. Furthermore, if the substance amyloid enhancing factor (AEF) is injected at the same time as the inflammatory stimulus, then amyloid deposition is accelerated. AEF is ill defined at the present, but has a protein component which is neither serum amyloid A nor serum amyloid P. The substance was originally isolated from amyloid deposits. In reactive amyloidosis, it appears that circulating serum amyloid A or locally produced serum amyloid A are not degraded fast enough within the extracellular micro-environment and the result is an accumulation of this degradation product of serum amyloid A. Analysis of the rate of degradation of serum amyloid A in the presence of macrophage or neutrophils has not shown any differences between patients with amyloidosis and those without. In the extracellular microenvironment, however, the cells may have different characteristics than circulating monocytes and neutrophils. Therefore it is still possible that the degradation enzyme(s) for serum amyloid A may not be produced fast enough or be deficient. The ability to clear amyloid protein breakdown products may be genetically determined.

Variation in the degradation rate of amyloid fibres could also be due to other proteins produced locally which inhibit efficient degradation by available enzymes. Hypersecretion of either serum amyloid P or GAG in the proximity of serum amyloid A proteins may inhibit their breakdown. It is interesting that we have previously shown that serum amyloid P can be a marker in amyloidosis associated with juvenile chronic arthritis.<sup>3</sup> The marker is not related to differences in the structure of serum amyloid P protein, but it is likely that this marker is associated with the promoter region of the serum amyloid P gene and therefore would

influence the level of secretion of serum amyloid P. This work is currently under study.

In summary, the clearance of serum amyloid A protein and its breakdown products is a crucial element in the development of amyloidosis and may be genetically determined. This hypothesis would explain the findings in our patients with juvenile chronic arthritis as described below, where only a small percentage of patients with identical illness have developed amyloidosis, and the regression rate is highly variable.

### Amyloidosis in juvenile arthritis

#### PREVALENCE

The prevalence of reactive amyloidosis varies between 1–10%. The British (7.4%) and German (3.1%) reports have higher prevalence compared with the American (1.8%) centres.<sup>4–6</sup> The reason for this is not entirely clear. It may be due to selection bias of various centres, length of follow up, possible differences in genetic background, and perhaps a tendency for more aggressive treatment early on in the disease in the USA. In Poland, where there is a more thorough reporting of cases of juvenile arthritis to a central board, the prevalence of amyloidosis is highest at 10.6%.<sup>7</sup>

The prevalence of amyloidosis is highest in systemic onset juvenile chronic arthritis compared with the other subgroups of juvenile arthritis. In the German series 92% of the patients were of systemic onset.<sup>5</sup> Our own data show that although amyloidosis is more frequently a complication of systemic juvenile chronic arthritis, polyarticular disease contributes 26% to the amyloidosis in our follow up group.<sup>8</sup>

The prevalence of amyloidosis is similar in adult rheumatoid arthritis.<sup>9</sup> In contrast, the prevalence in other inflammatory diseases like systemic lupus erythematosus and inflammatory bowel disease are much lower.<sup>10</sup>

#### CLINICAL FEATURES

Amyloidosis is usually suspected when proteinuria occurs. In the initial stages the proteinuria may be intermittent. The

patient is unwell, out of proportion to his/her inflammatory disease. Hypertension usually occurs later as a result of decreasing renal function. Abdominal discomfort due to oedema of the bowel may occur. Splenomegaly is found in about 60% of patients; however, the spleen is involved in all patients shown to have reactive amyloidosis by scanning techniques or at postmortem examination.<sup>11</sup>

#### LABORATORY FEATURES

There is invariably evidence of a raised acute phase response, that is, anaemia, raised erythrocyte sedimentation rate and C reactive protein, hypergammaglobulinaemia, and reduced albumin. Interestingly, immunoglobulin deficiency may also be seen in amyloid patients. In the Polish series there were 33 amyloidosis patients with immunoglobulin deficiency, particularly IgA and IgG, and these patients have the highest mortality.<sup>12</sup> Treatment with chlorambucil may contribute to hypogammaglobulinaemia and overwhelming infection may occur in these patients. A small amount of immunoglobulins may be lost due to urinary loss.

#### METHODS OF DIAGNOSIS

The definitive diagnosis of amyloidosis has, until very recently, relied upon the histological findings of congophilia on tissue biopsy specimens. The main source of tissue was rectal biopsy. More pleasant and reliable sites to biopsy include subcutaneous fat and the gums. Renal biopsy may be hazardous and the incidence of perinephric haematoma is not insignificant. There were three such cases in our series of 25 renal biopsies for amyloidosis. The cause of the excessive bleeding is due to the amyloid infiltration of the submucosa of blood vessels and thus reducing their contractability. Furthermore, a number of workers have demonstrated a prolonged bleeding time in these patients.<sup>13</sup> Bleeding diathesis may further occur as a result of reduced hepatic synthesis of clotting factors, although these have not been systemically measured.

In 1988 Hawkins *et al* described a new non-invasive isotope method of diagnosing amyloidosis.<sup>14</sup> The basis of this investigation relies on the high affinity of serum amyloid P for all types of amyloid fibril. In patients with amyloidosis when radioiodinated isologous serum amyloid P is given intravenously it rapidly leaves the vascular compartment and localises within the amyloid deposits, that is, a rapid plasma clearance of serum amyloid P is seen in amyloidosis. The distribution of labelled amyloid deposits is demonstrated by scintigraphy by the gamma camera, usually performed after 24 hours. The whole body retention of radioactivity is increased and this is measured indirectly as an inverse of the urinary isotope excretion over a seven day period. This technique has become essential in our investigation of the juvenile chronic arthritic in whom a diagnosis of amyloidosis is suspected. It has been useful in diagnosis, monitoring the response to treatment, and in revealing unsuspected organ deposits, particularly adrenal infiltration. This infiltration is important to recognise as it may be responsible for the collapse seen in amyloidosis sufferers with infection.

#### TREATMENT OF AMYLOIDOSIS

Colchicine is known to prevent and ameliorate the progression of amyloidosis in sufferers of familial Mediterranean fever before the onset of nephrotic syndrome.<sup>1</sup> With established nephrotic syndrome, colchicine is no longer effective. Dimethylsulphoxide (DMSO) has been extensively evaluated. It has been suggested that it may be effective in dissolving subunit proteins.<sup>15</sup> Most experience, however,

suggests that it is ineffective and furthermore, extremely unpleasant owing to the odour which is released after ingestion/topical application.

To date, the most effective method of management is by cytotoxic treatment. The aim is to completely repress the acute phase response and thereby reduce the raised concentrations of serum amyloid A. Ansell began using chlorambucil for the treatment of amyloidosis complicating juvenile chronic arthritis in the early 1960s. In the report of Schnitzer and Ansell it was seen that disease activity was controlled within one to three years of treatment.<sup>4</sup> Of all patients who had proteinuria at onset 64% had no proteinuria after three years or more. Berglund *et al* reported an improvement in survival in 14 patients with rheumatic diseases and renal amyloidosis with alkalinising agents in particular chlorambucil.<sup>16</sup> Ahlem *et al* found a five year survival rate, which improved from 27% in untreated controls to almost 90% in 22 patients who took part in a randomised prospective trial of treatment with variety of cytotoxic agents.<sup>17</sup>

Our own data confirm the improved survival in those treated with chlorambucil. At our 15 year follow up, 68% of chlorambucil treated patients with juvenile chronic arthritis and amyloidosis were alive in contrast to no patient in a non-cytotoxic treated group. Chlorambucil is used at a dose of 0.1–0.12 mg/kg/day. It is given as a single oral dose and well tolerated by the patient. Bone marrow toxicity may occur and needs to be monitored. It is usually reversible and rarely requires cessation of treatment. In our series of 79 patients, there was only one (1.75% incidence) who developed acute myelomonocytic leukaemia. This particular patient had previously received 3 g of azathioprine, which may contribute to the overall oncogenic effect, and died with advanced renal failure.

With the much improved survival figures, fertility status of the patient has been a clinical problem. No male patient in our series fathered a child. This infertility in male patients is further supported by other series.<sup>18</sup> In our female population premature ovarian failure occurred in six women. There were, however, three women who had uncomplicated and successful pregnancies.

#### CAUSE OF DEATH

The vast majority of patients with juvenile chronic arthritis that was complicated by amyloidosis died with renal failure (84%). Patients are at risk of developing acute renal failure even when the amyloidosis is controlled because of the impaired renal function. Twenty five percent had renal fibrosis and hypertension. Acute tubular necrosis has been described.<sup>19</sup> Infection is the second commonest cause of death, usually due to bacterial septicaemia. Immunosuppression and adrenal insufficiency are contributory. The nephrotic syndrome itself may be immunocompromising due to the urinary loss of immunoglobulin.

#### REGRESSION OF AMYLOIDOSIS

There have been case reports of regression of amyloidosis from repeat renal biopsy and postmortem studies. In experimentally induced amyloidosis in mice, amyloid deposits regress and disappear after cessation of the stimulus. With the advantage of the serum amyloid P scan method, we were able to demonstrate the absence of amyloid deposits in four individuals in remission of their juvenile chronic arthritis, all having previous histological evidence of amyloidosis. In addition, one patient who was scan positive became scan negative one year after remission. The rate of regression is highly variable, however, and this is currently the subject of further studies.

## Conclusions

Despite the progress in the understanding of the pathogenesis of amyloidosis and also the diagnostic field, many questions remain unanswered. The most important clinical question is that of a safe and effective drug for the control of amyloidosis. To date, chlorambucil remains the single agent which has been used to improve survival significantly. Scanning with serum amyloid P labelled with I<sup>123</sup> has facilitated non-invasive evaluation of a potentially life threatening complication of juvenile chronic arthritis.

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