Genetic factors in amyloidosis

P. K. THOMAS

From the Royal Free Hospital and Institute of Neurology, London

The variety of different classifications that have been suggested for the disorders that are characterized by the deposition of amyloid reflects the inadequate knowledge that so far exists as to the origin and mechanisms of amyloid formation. The precise nature of amyloid has not been established. It is recognized (see Cohen, 1972) by its tinctorial properties and by the presence in electron microscope preparations of rigid non-branched fibrils approximately 10 nm in diameter. Amyloid deposits contain mucopolysaccharide and small amounts of immunoglobulin. The composition of amyloid varies between tissues and between clinical types. It is uncertain whether this is due to differences in the composition of the fibrils or whether it is related to varying quantities of associated substances. Amyloid may be widespread throughout the body or discretely localized. Although the distinction between amyloidosis secondary to other diseases and primary amyloidosis has been questioned, this remains clinically useful. It is also helpful to separate the inherited amyloid syndromes. The proposed division of the amyloidoses on a histopathological basis into pericollagen and perireticulin forms (Missmahl and Hartwig, 1953/1954; Heller *et al*, 1964a) has not been generally accepted.

The unsatisfactory situation with respect to classification extends to the inherited amyloidoses. Attempts have been made to apply the subdivision into pericollagen and perireticulin forms to this group (Gafni *et al*, 1964; Heller *et al*, 1964b). In this review, a broad clinical subdivision based on the anatomical system primarily affected by the disease process will be adopted. Other recent reviews of the inherited amyloidoses are those of Mahloudji *et al* (1969) and Cohen (1972).

Neurological syndromes

Symmetrical polyneuropathies

Portuguese type polyneuropathy. Andrade (1952) delineated 'a peculiar form of peripheral neuropathy' that afflicted the inhabitants of the fishing town of Póvoa de Varzin in the Oporto district of Portugal, where it was known as *mal de pésinhos* (foot disease). A necropsy on a case of this type was earlier referred to in a report by Wohlwill (1942). Andrade and later other workers from Portugal (see Andrade *et al*, 1969) established the salient clinical features, drew attention to the familial nature of the disorder, and recognized that it was a manifestation of primary amyloidosis. Although not restricted to the Oporto district, it is most common in that part of Portugal; 173 families are known to be affected (Andrade, 1970). Cases of Portuguese origin have been reported from Brazil (Julião and Mignone, 1955; de Mello, 1959; Julião *et al*, 1974), Germany (Erbslöh, 1961), and the United States (Munsat and Poussaint, 1962).

The condition develops insidiously, rarely abruptly (Andrade, 1963; Antunes *et al*, 1963). Loss of thermal and pain sensibility distally in the lower limbs is usually the first symptom. The hands are similarly affected at a later stage. Spontaneous pain and tingling paraesthesiae may occur. The loss of pain sense may result in persistent cutaneous ulceration. Loss of tactile, postural, and vibratory sensation follows. Autonomic changes are an early feature and include impotence, disturbances of gastrointestinal (Rosario *et al*, 1963) and bladder function, pupillary abnormalities, and distal anhidrosis in the limbs. Distal muscle weakness and denervation atrophy, again of earlier onset and of severer degree in the lower limbs, is a later manifestation than sensory loss and autonomic disturbance. The tendon reflexes are frequently preserved until the more advanced stages of the

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Reprint requests to: Royal Free Hospital, Pond Street, London NW3 2QG.

disease. The condition is steadily progressive; death usually occurs within 10 years of the onset of the symptoms.

Vitreous opacities may develop (de Andrade, 1961) and electrocardiography may reveal conduction defects and cardiac dysrhythmias (Coelho and Pimentel, 1961; Andrade *et al*, 1965). Amyloid involvement of the kidneys is usually detected at necropsy, but impairment of renal function during life is not documented. Pathological studies (da Silva Horta, 1955; da Silva Horta and Trincão, 1963) also demonstrated widespread vascular involvement, and amyloid deposits in the peripheral nerves and sympathetic ganglia, spleen, cardiac muscle and smooth muscle of the gut, and in the skin. It has been claimed that the amyloid is of the pericollagenous form (da Silva Horta *et al*, 1964). The dissociated pain and temperature sensory loss and the prominence of the autonomic symptoms can be related to a predominant loss of unmyelinated and small myelinated axons (Dyck and Lambert, 1969; Thomas and King, 1974). The ultrastructural features of amyloid neuropathy have been considered by Coimbra and Andrade (1971a; 1971b) and Thomas and King (1974).

A genetic study of 623 individuals from 148 sibships was performed by Andrade *et al* (1969) and on a smaller series of cases by Becker *et al* (1964). An autosomal dominant mode of inheritance was found. Of the 249 affected individuals in the series reported by Andrade *et al* (1969), 153 were male and 96 female. The average age of onset was 33 in males and 44 in females. With respect to the sex ratio, there was a predilection for males when all families with at least one affected individual were considered, but the ratio approximated to 1:1 when families with at least two affected members were analysed. It was assumed that at the time of registering sibships, there was a bias towards registering those with a male propositus, and it was concluded that there was no difference between the sexes with regard to the degree of penetrance. Discordance between the sexes was restricted to the age of onset. The age of onset exhibits considerable variability. Becker *et al* (1964) gave a histogram for the 29 cases that they studied, which ranged from 15 to 60 years. Males and females were not separated. Calculation from their results gives a mean and standard deviation of 34.5 ± 11.1 .

The geographical concentration of the affected families in Portugal presents an anomalous situation. It is among the largest localized expressions of a conspicuously deleterious dominant mutation known. It seems likely that the families are all the result of a single mutation. If not, the occurrence

of a mutation so frequently in a particular area would require explanation. Linkage studies have not so far been reported, but might establish the homogeneity of the disease in so large a population. The genetic, social, and economic factors permitting the spread of the disease are not yet understood. Andrade *et al* (1969) suggested that the higher age of onset in females might contribute to the persistence of the gene despite the selection pressures operating against it.

Japanese cases. Araki *et al* (1968) reported an extensive family from the Kyushu area of Japan in which 25 individuals from four generations were affected by a peripheral neuropathy related to primary amyloidosis with features similar to those of the Portuguese variety. The inheritance was of autosomal dominant pattern with an equal sex ratio. The age of onset was between the ages of 30 and 47 and death occurred after about 10 years. It is of interest that the Kyushu area was the site where the Portuguese first set up a trading post in 1549, although no Portuguese ancestry could be traced in this family (Araki and Kuroiwa, 1970). Two further families were subsequently discovered in the Kyushu area (Araki and Kuroiwa, 1970). Reports of familial amyloid neuropathy from other areas of Japan are those of Nakao *et al* (1966), Yamazaki *et al* (1969), and Izawa *et al* (1969).

Iowa type. Van Allen *et al* (1969) described a family from Iowa originating from the British Isles with generalized primary amyloidosis of probable autosomal dominant inheritance. Histological confirmation was obtained in eight members. The onset of the disorder was in the third and fourth decades and the average duration from the onset of symptoms to death was 12 years. Peripheral nerve involvement was a prominent feature, giving rise to an approximately symmetrical sensorimotor polyneuropathy affecting the lower limbs earlier and more severely than the upper. The initial symptoms were lancinating pains, paraesthesiae, and weakness in the legs. Loss of pain sense occurred early; in more severe cases, loss of other sensory modalities, distal muscle weakness, and wasting and tendon areflexia developed. Symptoms suggestive of autonomic involvement were also present but were less obtrusive than the Portuguese cases. Nephropathy was common, in contrast with the Portuguese cases, and renal failure was the most frequent cause of death. There was also an unusually high incidence of duodenal ulcer, and this was present in six of the eight pathologically verified cases. Peptic ulcer has been recorded in primary

amyloidosis; in a case reported by Lindsay and Knorp (1945) the ulcer wall was infiltrated with amyloid.

A further comparable family has recently been reported from Spain by Gimeno *et al* (1974).

Other families. A family with features similar to the Portuguese form has been reported from Germany (Delank *et al*, 1965). In one patient, culture of a bone marrow biopsy yielded an extra chromosome with a subterminal centromere in 10% of the mitoses (Missmahl and Siebner, 1965). The significance of this is uncertain. The cases of Greek origin from two separate kinships reported from the United States by Dyck and Lambert (1969), and the case from another Greek family reported by Thomas and King (1974), all closely resembled the Portuguese type. The same is probably true of a family reported from Poland (Kulisiewicz *et al*, 1964). Kantarjian and DeJong (1953) described a family from the United States in which a man and his two daughters were affected. The features again in general resembled the Portuguese type, with an insidious onset after the second decade, as did those in a further family from the United States (Shulman and Bartter, 1956; von Sallmann *et al*, 1960), in which particular attention was paid to a description of vitreous opacification due to amyloid (Kaufman, 1958; Kaufman and Thomas, 1959; Paton and Duke, 1966).

A case reported from England in 1929 by de Bruyn and Stern as hypertrophic polyneuropathy of Dejerine-Sottas type was almost certainly one of amyloid neuropathy. The histology was later reviewed by de Navasquez and Treble (1938). The symptoms began at the age of 49 and consisted of a distal polyneuropathy with prominent autonomic features and associated cardiac failure. The peripheral nerves were thickened. Three sibs had been similarly affected and all died about three years after the onset of symptoms. Another family has recently been reported from England by Zalin *et al* (1974). Three brothers were affected. Although autonomic features occurred, the cases differed from the Portuguese variety in that dissociated sensory loss was not detected and cardiac arrhythmias and congestive cardiac failure occurred. The age of onset was also later, being 52, 54, and 69. A later age of onset and associated cardiac involvement also characterized the cases of hereditary amyloid polyneuropathy reported from Scandinavia by Andersson (1970). Vitreous opacities were a feature. Eighteen members were affected in two families, in which the inheritance was probably autosomal dominant in pattern, although both families con-

tained consanguineous marriages. The average age of onset was 45 in males and 10 years later in females.

A family was reported by Hicks in 1922 in which the salient features were perforating ulcers of the feet, shooting pains and deafness. Pain and temperature sensation was lost in the feet and the tendon reflexes were abolished in the legs. A necropsy of one case from this family, in which the inheritance was probably of autosomal dominant pattern, was reported by Denny-Brown (1951). He concluded that the disease was due to a degeneration of dorsal root ganglion cells. Although no amyloid was found in the peripheral nerve trunks or outside the nervous system, the dorsal root ganglia contained perivascular deposits identified as amyloid which were considered to be secondary. The status of this family is therefore uncertain.

Carpal tunnel syndrome and polyneuropathy

Indiana family. Two cousins from a family of Swiss descent which had migrated to the United States in 1883 were found to have vitreous opacities associated with a peripheral neuropathy that predominantly affected the hands. A diagnosis of amyloidosis was established in both by gingival biopsy (Falls *et al*, 1955). Both cases later died and were found to have widespread perivascular and cardiac deposits. The vitreous opacities were also shown to be amyloid (Jackson *et al*, 1960).

The family was extensively investigated by Rukavina *et al* (1956a; 1956b), and later reviewed by Jackson and Block (1970). Out of 66 members investigated, 29 were found to be affected. The onset was in the third or fourth decade with symptoms of the carpal tunnel syndrome. Sensory loss later appeared more diffusely in the distal part of the upper limbs and subsequently distally in the legs. Autonomic disturbances were associated and the vitreous opacities usually appeared in the sixth decade. Cardiac failure was a late feature. The inheritance was of autosomal dominant pattern (Jackson *et al*, 1960).

Maryland family. Mahloudji *et al* (1969) reported a large kindred that had originated from a couple of German origin who had married in about 1775. The clinical features were closely similar to the Indiana cases, but no genealogical connection could be established. A total of 146 individuals in seven generations was affected, of which 59 were alive; 53 were examined. The mean age of onset of symptoms was 43 with a range of 15 to 66, and did not differ between males and females. The family had originally been investigated by Schlesinger *et al* (1962).

The initial presentation was usually with the carpal tunnel syndrome (Mahloudji, 1968) and sensory loss was at first confined to the distribution of the median nerve. The flexor retinaculum was shown to be infiltrated with amyloid (Lambird and Hartmann, 1969). Others presented with weakness and wasting of the small hand muscles. As the disease progressed, the neurological deficit extended outside the territory of the median nerve in the upper limbs and involved the lower limbs, where it initially gave rise to sensory loss and later motor signs and tendon areflexia. The disease advanced more rapidly and was of greater severity in males. In females, even those in the older age groups, the condition often remained confined to the hands. Autonomic changes and cardiac involvement were rare, as was the occurrence of vitreous deposits.

Cranial neuropathy. Meretoja and Teppo (1971) described examples of a familial amyloid syndrome in which a cranial neuropathy and a lattice corneal dystrophy were the principal manifestations. The neuropathy particularly affected the facial nerves. Renal biopsy in four patients revealed amyloid deposition predominantly within the glomeruli (Meretoja *et al*, 1972). Necropsy demonstrated that amyloid was present in relation to blood vessels in most organs. There was slight cardiac involvement. The endoneurium and perineurium of the peripheral nerves were markedly affected, particularly in the cranial nerves.

Presenile dementia with amyloid cerebral angiopathy. Corsellis and Brierley (1954) described two cases of an unusual form of presenile dementia, in one of which a sib was probably affected by the same condition. Pathological study demonstrated an amyloid angiopathy restricted to the meningeal and small cerebral vessels, and widespread amyloid-containing plaques in the brain. These changes were identified as corresponding to those described in patients from a family with presenile dementia and spastic paraparesis by Worster-Drought *et al* (1940; 1944) of probable autosomal dominant inheritance. Similar families were recorded by van Bogaert *et al* (1940) and Lüers (1947), and the subject has been reviewed by Gerhard *et al* (1972).

Hereditary cerebral haemorrhage. Guðmundsson *et al* (1972) described a family from Iceland in which there was a high incidence of presumed cerebral haemorrhage over four generations. It was observed as a cause of death in 54% of all deaths in this family. The mean age of death from cerebral haemorrhage was approximately 44 in the

first and second generations, 29.6 in the third and 22.5 in the fourth. A number of cases had recurrent cerebral haemorrhages. Necropsy was performed in five cases and confirmed cerebral haemorrhage. Amyloid deposition was found in the walls of the cerebral arteries; other vessels were not involved. Dementia was not a feature.

Visceral syndromes

Familial Mediterranean fever. Heller *et al* (1958) defined familial Mediterranean fever as an inherited disorder characterized by relapsing febrile episodes and in which renal amyloidosis could be a terminal event. The condition had previously been incompletely delineated and had been given a variety of designations. Mamou and Cattani (1952), from observations in North Africa, had recognized that cases of 'la maladie periodique' were frequently accompanied by renal disease and noted their familial occurrence. Mamou (1955) recorded the development of amyloidosis. Later studies by Heller and his associates (Heller *et al*, 1961; Blum *et al*, 1962; Sohar *et al*, 1967) characterized the disorder more precisely. Two phenotypes were recognized. In phenotype 1, the course of the disease is punctuated by self-limited febrile episodes beginning in childhood lasting 24–48 hours and occurring at irregular intervals either in isolation or accompanied by peritonitis, pleuritis, synovitis, or erysipelas-like erythema. Peritoneal attacks are the most frequent, being observed in 95% of cases. Attacks of synovitis occur in 78% and pleuritic attacks in 40%. The cutaneous manifestations either occur independently or in relation to an attack of synovitis, usually monoarticular. In phenotype 2, which is less common, amyloidosis is the initial manifestation and gives rise to nephropathy or intestinal malabsorption. There is therefore no direct relationship between the febrile attacks and amyloidosis, but death is usually caused by renal failure in both groups. It usually occurs under the age of 40, sometimes in early childhood. Necropsy studies show that in addition to the kidneys, the spleen, adrenals, lungs, and gastrointestinal tract are also affected. There is only minimal cardiac involvement and hepatic involvement tends to be limited to the blood vessels. The amyloid is stated to be 'perireticulin' in type. The fine structure of the amyloid fibrils, observed in renal and rectal biopsies, is similar to other types of amyloid (Cohen *et al*, 1962).

The disorder predominantly affects Sephardic Jews, but also Armenians and Arabs (Sohar *et al*, 1967), and Turks (Ozdemir and Sokmen, 1969). It is considered to be due to a single autosomal

recessive gene (Sohar *et al*, 1961; Heller *et al*, 1961). For sibs born to unaffected parents, the proportion of affected sibs was 0.184 (Sohar *et al*, 1967). This value is low for this type of study. It is possible that this was contributed to by the exclusion of unproven cases and by the fact that young individuals might have developed the disease later. However, the low figure could indicate that an environmental factor is involved.

First-cousin marriages occurred in 16% (Sohar *et al*, 1967), a significantly greater rate than in the general Jewish population in Israel. The gene frequency was estimated at 0.022 for the Israeli Sephardic population, with a homozygote incidence of 1:2000. On the other hand, figures derived from first-cousin marriages are difficult to interpret when the subgroups which possess the gene have a high incidence of first-cousin marriages.

No published information appears to be available concerning the distribution of the two phenotypes within families. It would be of interest to know whether these are concordant or discordant in sibships resulting from first-cousin marriages, and what differences exist between sibships from unrelated first-cousin marriages.

No sex difference was found as to the age of onset or death. Cytogenic studies on five patients revealed no significant abnormalities (Krey and Cohen, 1965).

Dominantly inherited recurrent febrile illness with amyloidosis. In one family from the series of cases reported by Sohar *et al* (1961) in which the disorder appeared in three consecutive non-consanguineous generations, the inheritance was possibly autosomal dominant in pattern. Families with 'periodic disease' in which the disorder affected three or more generations have also been described (Reimann *et al*, 1954; Benhamou *et al*, 1955; Bickel and Lasserre, 1957).

Two families have been documented with a clinical syndrome similar but not identical to familial Mediterranean fever, but in which the inheritance appears to be autosomal dominant in type. Bergman and Warmenius (1968) described a Scandinavian family originally reported by Nilsson and Floderus (1964) as hereditary periodic disease. Four individuals were affected, a father and three sons by two wives. The disorder was characterized by attacks of abdominal pain and fever which began in childhood. These were of longer duration than in familial Mediterranean fever, persisting for several days or weeks. Pleuritic pain, synovitis, and cutaneous involvement were not a feature. The nephrotic syndrome developed in adult life.

Necropsy on two cases revealed amyloid deposition in much the same distribution as in familial Mediterranean fever. The second family, of Italian origin, was reported from the United States (Reich and Franklin, 1970). The proband developed intestinal amyloidosis at the age of 64. He was unchanged at the age of 80 without clinical evidence of renal involvement. His daughter and granddaughter suffered from recurrent attacks of abdominal pain and fever dating back to childhood.

The early family documented by Maxwell and Kimbell (1936) bears some resemblance to this group of cases. Three brothers were described with renal amyloidosis who died in the fifth decade of life. A further brother was unaffected. All three affected individuals had been subject to frequent febrile attacks in childhood. A follow-up study on this family in 1967 (Mahloudji *et al*, 1969) established that the son of one of the affected brothers was subject to recurrent febrile episodes of unknown origin in early childhood. He developed the nephrotic syndrome in the fourth decade and died at the age of 69. Necropsy demonstrated amyloid deposits, mainly in the kidneys and spleen. Two of his five children have had frequent febrile episodes accompanied by transient joint pains and 'slight maculopapular rashes'.

Recurrent febrile episodes, urticaria, deafness, and amyloidosis. A more complex constellation of clinical features, but again encompassing recurrent febrile episodes in association with predominant renal amyloidosis, was observed in a family from Derbyshire studied over five generations by Muckle and Wells (1962). Nine individuals suffered from the disorder, of whom four were personally investigated. The inheritance was considered to be of autosomal dominant pattern. The condition consisted of febrile episodes ('aguey bouts') with an onset during adolescence, lasting usually less than 36 hours, accompanied by malaise, rigors, urticaria or angioneurotic oedema, and pains in the limbs. Of the four cases that were examined, all had sensorineural deafness and pes cavus. One had sensory loss over the legs and lower trunk with stabbing pains in the limbs, and preserved tendon reflexes. A peripheral neuropathy was diagnosed, but was not confirmed by nerve conduction or biopsy studies, and it may be relevant that there was a previous history suggestive of retrobulbar neuritis. Nephropathy was present in three of the cases, possibly four, and one showed hyperglycinuria. Three died from uraemia. Necropsy on two showed renal and adrenal amyloid deposits, together with deposits in the liver and testes in one.

The cochlear nerve was stated to be atrophic in both cases with 'absence of the organ of Corti and vestibular epithelium' without amyloid deposits. Kennedy *et al* (1966) later described a solitary case from the same geographical area, but no relatives were traced. This was a male aged 56 with an 11-year history of febrile episodes lasting 24 hours on each occasion, associated with urticaria, leucocytosis, and a raised erythrocyte sedimentation rate. He showed bilateral pes cavus but no evidence of neuropathy. The nephrotic syndrome developed after 10 years, at which time sensorineural deafness was noted. Amyloidosis was demonstrated on renal biopsy. Death occurred from uraemia and at necropsy, in addition to renal amyloid, deposits were present in the adrenals, liver, testes, lungs, and other sites.

A family with similar features was reported from the United States by Black (1969). The index case, who was aged 22, suffered from intermittent episodes of limb pains associated with fever and an urticarial rash. She was deaf, but did not have pes cavus or neuropathy. Amyloidosis was demonstrated by renal biopsy. In the family study, which covered three generations, five members had a history of nephropathy, deafness, urticaria, and limb pains.

Nephropathy and hypertension. The first description of inherited amyloidosis was that of Ostertag (1932). The family was reviewed 15 years later (Ostertag, 1950). Five members from three generations were affected by renal amyloidosis, hypertension and hepatosplenomegaly, and one other relative who died from renal disease was possibly affected. Amyloidosis was confirmed by necropsy in two individuals. It is somewhat doubtful whether this family justifies separate categorization, as an appreciable number of all cases of renal amyloidosis develop hypertension.

Cardiac amyloidosis. Fredericksen *et al* (1962) reported a family in which four out of 12 sibs developed primary systemic amyloidosis manifested by progressive heart disease beginning in the fourth or fifth decade and leading to death from cardiac failure within two to six years. Other generations were not affected, although documentation in the parents was inadequate. Consanguinity is not mentioned. Trivial neurological symptoms were present, with transient paraesthesiae in the hands in three cases. Two other sibs were possibly affected. Moderate cardiac enlargement was present. Electrocardiography showed conduction defects or a pattern of left ventricular hypertrophy or strain, and

catheter studies demonstrated increased right atrial and pulmonary wedge pressures. At necropsy, there was extensive amyloid deposition in the myocardium and endocardium, with lesser involvement of other organs.

In another family with amyloid heart disease, Allensworth *et al* (1969) reported persistent atrial standstill in three sibs whose symptoms had developed in the third decade. A further sib was possibly affected. The father had died from heart disease when aged 55, but details were not given. Cardiac enlargement was present in the three confirmed cases. All had slow heart rates and mild congestive failure. Electrocardiography showed regular QRS complexes but absent P waves. Intracardiac recording confirmed the absence of atrial activity. Intracardiac atrial stimulation in two cases was ineffectual. One patient suffered from Stokes-Adams attacks that were successfully treated by a pacemaker.

The status of the Swiss family described by Klein *et al* (1962) is uncertain. Two brothers were stated to have had vitreous opacities and 'nodular periarteritis' of the retina. Minor neurological features were present, and also petechial and larger haemorrhages into the skin. Progressive cardiac failure ensued and led to death 10 and 12 years after the onset of symptoms. Necropsy revealed amyloid deposits in the blood vessels in all organs examined.

Miscellaneous syndromes

Lattice corneal dystrophy is a rare disorder inherited as an autosomal dominant trait and manifested by progressive corneal opacification from a network of branching filaments or other types of deposit. These have been shown to be amyloid (Klintworth, 1967; Smith and Zimmerman, 1968). Except for the recent reports of an association between cranial neuropathy and lattice corneal dystrophy (Meretoja and Teppo, 1971), where widespread amyloid deposits have been demonstrated, there has been no clinical evidence to suggest involvement of other organs. Necropsy studies have not so far been performed on cases of isolated lattice corneal dystrophy.

Localized cutaneous amyloidosis. Isaak (1950) recorded two sibs of Russian Jewish extraction with long-standing psoriasis. Both developed localized cutaneous amyloidosis in later life. Sagher and Shanon (1963) described naevoid lesions on the back of an elderly woman, her son, and the son's daughter. The son also had psoriasis.

Amyloid was demonstrated in the lesion in the grandmother and her son. Finally, de Souza (1963) reported four sibs aged 19 to 34 with bullous cutaneous lesions, most frequently situated over joints, beginning in early adolescence and shown to be associated with amyloid deposits in two cases. There was no record of any examination of the parents.

Medullary carcinoma of the thyroid. Sipple (1961) focused attention upon a syndrome that now sometimes bears his name in which there is an association between pheochromocytoma, parathyroid adenoma, and medullary carcinoma of the thyroid. It has also been referred to as multiple endocrine neoplasia, type 2 (Steiner *et al*, 1968), type 1 being the association between tumours of the pituitary, pancreas, and parathyroid. These authors drew attention to the local deposition of amyloid that may occur in medullary carcinoma of the thyroid. The familial occurrence of Sipple's syndrome has been documented in a number of reports, including those by Cushman (1962), Nourak (1964), Schimke and Hartmann (1965), and Sarosi and Doe (1968), in all of which there were amyloid-containing medullary thyroid carcinomas. A large kindred was investigated by Steiner *et al*. (1968). Out of 186 subjects, 10 proven and five possible examples of pheochromocytoma were found, two instances of parathyroid hyperplasia, and five of medullary thyroid carcinoma, all of which contained amyloid. They concluded that the inheritance was of autosomal dominant pattern.

Down's syndrome. Amyloid deposition, particularly in the brain, heart, aorta, and pancreas occurs with some frequency in later life in normal individuals (Wright *et al*, 1969). In Down's syndrome, deposits develop at a substantially earlier age (Schwarz, 1968; Gonzalez-Cueto *et al*, 1968). The occurrence of amyloidosis of cerebral vessels in association with giant cell arteritis has recently been documented in an elderly patient with this syndrome (Reid and Moloney, 1974).

Conclusions

In the absence of biochemical distinctions, the nosography of the inherited amyloidoses must at present depend largely upon clinical subdivisions. In the broad classification adopted here, the disorders have for convenience been grouped according to the anatomical system that is predominantly affected. It is evident that the amyloid syndromes display considerable heterogeneity. However, they overlap. Thus in the Iowa type classified with

the hereditary amyloid neuropathies (van Allen *et al*, 1969; Gimeno *et al*, 1974), renal involvement was frequent and was the usual cause of death. In the English (Zalin *et al*, 1974) and Scandinavian (Andersson, 1970) families with neuropathy as the predominant feature, cardiac involvement was a common finding.

In certain of the conditions discussed, such as medullary carcinoma of the thyroid and Down's syndrome, amyloid deposition is merely an incidental aspect of the disorder. In those conditions in which generalized or localized amyloid deposition occupies a more central position in the clinical syndrome, an autosomal dominant inheritance has been established or suggested in the majority. An autosomal recessive inheritance has so far only been recognized in familial Mediterranean fever. In the family with hereditary amyloid heart diseases reported by Fredricksen *et al* (1962), the disorder was confined to a single sibship, raising the possibility of recessive inheritance. This could also be true in sporadic examples of primary amyloidosis.

The dominantly inherited amyloidoses comprise a number of geographically widely scattered families with clinical pictures that do not show consistent differences between some families. The families that do not show consistent differences are not necessarily harbouring mutations at the same locus, or the same mutation at any particular locus. However, many of these dominantly inherited clinical syndromes are sufficiently different from each other and the clinical manifestations of each sufficiently consistent to indicate that separate main genes are likely to be involved. In hereditary amyloidosis with peripheral neuropathy as the salient manifestation, consistent differences exist in the pattern of the disease between the Portuguese type (Andrade, 1952), the Indiana and Maryland families in which presentation with the carpal tunnel syndrome is a conspicuous feature (Rukavina *et al*, 1956a, b; Mahloudji *et al*, 1969), and in the form in which a cranial neuropathy is associated with lattice corneal dystrophy (Meretoja and Teppo, 1971). Tourtellotte *et al* (1963), on the other hand, concluded that the Portuguese and Indiana forms of amyloidosis were likely to be the same disease. The frequency of occurrence of nephropathy in the Iowa type (van Allen *et al*, 1969; Gimeno *et al*, 1974) marks it out as distinct, as do the late onset and frequency of cardiac involvement in the Scandinavian and English families of Andersson (1970) and Zalin *et al* (1974). Even where the clinical manifestations in different families are similar, there is no firm evidence to suggest that the mutations are the same except in the Portuguese and possibly the Japanese

forms. Establishment would require linkage or definitive biochemical studies. Small differences between families may be due to sampling artefacts where intrafamilial variation is large, to environmental effects, or to main gene differences.

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