Familial Amyloidosis with Polyneuropathy

A Clinical Study Based on Patients Living in Northern Sweden

BY

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This account is based upon studies stated below. It also contains informations, based on the whole patient material, which have not been published previously, particularly concerning the development of the disease and about genetics.


These papers will be referred to in the text by their Roman numerals.
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INTRODUCTION

A few isolated cases of primary amyloidosis with polyneuropathy had been described earlier (17, 30, 43), when several cases were reported in 1952 from Portugal (1). The disease was confined then as a clinical entity. The familial occurrence of the disease was pointed out also. Only a few reports of similar familial amyloidosis were to be found before from other countries (18, 19), when some cases of this disease were diagnosed in 1965 at the Department of Internal Medicine, University Hospital, Umeå (I). Since then further cases have gradually been found in the north of Sweden. Most of them have been familial. Also cases, so far considered sporadic, have been diagnosed.

One isolated case of primary amyloidosis, where peripheral polyneuropathy was the characteristic manifestation had been reported from Finland in 1954 (33), while familial occurrence of amyloidosis with polyneuropathy had not been previously reported from the Nordic Countries (Denmark, Finland, Iceland, Norway and Sweden). It was therefore considered justified to analyse more closely the character of the disease on the basis of the existing material in northern Sweden. This material comprised 60 patients, of whom 42 were familial.

The aim was in the first place to study the clinical manifestations of the disease and the possibilities of diagnosing the disease. As the histological proof of the amyloid substance is of decisive importance for the diagnosis of amyloidosis, and as the deposition of amyloid in various organs is probably of importance for the clinical manifestations, particular attention was given to the histopathology of the disease. The familial occurrence was also studied. Symptoms of the disease were not confined to the peripheral nerves but also connected with many other organs. Certain disturbances, for example in connection with function of the urinary bladder, peripheral circulation, and to a certain extent also function of the gastrointestinal tract, were studied in greater detail. The polyneuropathy was studied with neurophysiological methods. Factors, which affect the time of survival from onset of symptoms till death, were watched. Questions concerning the conformity of the cases under observation, with those,
which were described in Portugal and other countries, were dealt with. Statistical genetic calculation was performed on the material which had been collected.

**MATERIAL**

The primary patients with the disease were discovered in the routine medical service at Umeå Hospital (I). Since the occurrence of this disease in northern Sweden had become more well-known, further cases were diagnosed also in other hospitals. These cases were kindly placed at disposal for this investigation. Two families were studied more closely in connection with the appearance of the disease. On the other hand, there was no complete inventory made concerning the total number of people suffering from the disease in the region.

The patient material for this account is listed in Table I. It comprised 60 patients.* The cases are designated in the table with clinical numerals, 1 - 60. Genetic numerals, referring to pedigrees, Figure 1 - 15, are also given as well as designations from previous publications. The cases were collected in accordance with the following three groups:

**Group 1.** Consecutive cases, which were diagnosed in northern Sweden from Autumn 1965 to Summer 1974. They had all polyneuropathy. Amyloidosis was confirmed by histopathological examination of biopsy material. The majority of the cases were diagnosed at the Departments of Medicine in Umeå and Skellefteå. Information of new cases was received also from the Department of Neurology, Umeå, and from hospitals in other parts of the region. In this group there were 49 cases. Sixteen of these cases had died by Summer 1974.

**Group 2.** Six cases of which 4 were relations to patients in group 1. They had died before this study started. Clinical data were taken from hospital records. Pathologico-anatomical diagnosis could be substantiated by re-examination of biopsy or autopsy material. This group included cases with the clinical numerals 5, 10, 21, 36, 45 and 54.

*Since the completion of this investigation, about 10 more cases have been diagnosed in the region.*
Group 3. Five cases, deceased close relations (siblings or children) to patients in group 1, without pathologico-anatomical confirmation of amyloidosis. According to hospital records, however, they had a typical clinical picture of advanced polyneuropathy. In the cases with clinical numerals 3, 4, and 35, amyloidosis was histopathologically confirmed in their brother or sister. In two cases, no. 12 and 13, there was a reliable report of serious polyneuropathy in one of their respective parents. Neither biopsy nor autopsy had been carried out on these patients. The diagnosis is discussed under the heading GENETICS.

Fortytwo of these 60 patients belonged to 15 families whose pedigrees are described in Figure 1 - 15. Eighteen were regarded as sporadic, clinical numerals 43 - 60.

In this account, the result of genealogical studies, especially regarding two families, Figure 1 - 2, is also presented. The material for these genealogical studies was collected by information from the patients themselves, from pastorates in various parishes and from the Provincial Archive in Härnösand as well as by information from two genealogists, Mr Ossian Egerbladh Ph.D., and Mr Bertil Lindqvist. Microfilmed copies of parish records available at the County Library in Umeå were studied personally by the author.

In addition to the aforementioned 60 cases, 20 members of family 1, and 50 members of family 2, were the subject of clinical examination by the author. Some of the seventy relations examined had clinical symptoms which agreed with those found in the amyloidosis patients. Despite repeated biopsies no amyloid, however, could be detected in those cases. They will be discussed under the heading GENETICS.

METHODS

Peripheral polyneuropathy

Diagnostic criteria of polyneuropathy were partly anamnestic information, partly findings at clinical examination.

A. Anamnestic information concerning dysesthesia, paresthesia.
and loss of sensibility as well as concerning progressive muscular wasting and weakness.

B. Findings at clinical examination pointing to sensory disturbances (tests by pin-prick, cotton-wool, hot and cold water in a testtube, and tuning fork and test of the sense of position) and motor disturbances (muscular atrophy and reduction of strength). Examination concerning spontaneous muscular fasciculations as well as tendon reflexes in arms and legs was performed.

These clinical examinations were supplemented in the majority of cases by neurophysiological examination. Electromyography and estimation of the motor conduction velocity were carried out on 34 patients according to methods described previously (III).

A grading of the symptoms and signs from the peripheral nerves was done clinically (III) + means slight, ++ moderate and +++ advanced degree of polyneuropathy. It should be pointed out that the gradation used was only semi-quantitative. It was used to give an approximate conception of the neuropathy at the time of the actual examination.

Amyloidosis
Examination concerning the occurrence of amyloid substance in biopsy specimens and autopsy material was performed according to methods described previously (V, VIII). Amyloidosis was considered confirmed if staining with alkaline Congo red (32) showed deposits of a substance, which in an ordinary light microscope gave a bright green colour when viewed in polarized light (28).

Statistics
The statistical studies comprised only calculations concerning median and mean values, standard error of mean, standard deviation, S.D., standard error of standard deviation, and mean difference. The significance of the difference between two means was calculated according to Fischers test.
RESULTS

Sex and Age Distribution

Of the 60 cases in the clinical material, 40 were men and 20 women, Table I. These numbers give the proportion of men:women as 2:1. Of the familial cases 27 were men and 15 women = 1.8:1. The cases considered as sporadic consisted of 13 men and 5 women. This gives the proportion of men to women as 2.6:1 in this group.

In 49 cases the diagnosis was established ante mortem by examination of biopsy specimens. Age at the time of examination when the diagnosis was established, can be seen in Tables I and III. The median age was 61 years and the mean age $59.8 \pm 12.9$ (S.D.). For 33 men the median age was 63.5 and the mean age $61.8 \pm 13.6$. Sixteen women had the median age of 59.5 and the mean age of $55.5 \pm 11.8$.

A comparison between familial and sporadic cases showed that for the 33 familial cases the median age was 61 years, and the mean was $60.1 \pm 13.2$ (S.D.), while the 16 sporadic cases had median age of 58.5 and a mean age of $59.1 \pm 12.7$.

In the group of familial cases 21 probands had at diagnosis a median age of 66 years and a mean age of $63.9 \pm 13.2$ (S.D.). For 12 secondary cases in this group the median age was 56 and the mean age was $53.5 \pm 10.8$. Statistically, the difference between probands and secondary cases in this respect was significant ($0.05 > p > 0.01$).

Age at Onset

The age at the time of the initial symptoms of the disease can be seen in Tables I and IV. For the 60 patients as a whole the median age in this respect was 53.5 years and the mean age $53.0 \pm 11.4$ (S.D.), range 29-75 years. For 40 men the median age was 55.5 and the mean age $54.4 \pm 11.9$. The median age for 20 women was 51.5 and the mean age $50.1 \pm 9.7$. The difference between men and women was not significant ($p > 0.1$).

When a comparison was made between the groups of familial
and sporadic cases no difference was found. The median age for 42 familial cases was 54 years and the mean age was $52.6 \pm 11.7$ (S.D.). For the 18 sporadic cases the median age was 54 and the mean age was $53.9 \pm 11.9$.

It must be pointed out that the times given regarding the onset of the disease in some cases were uncertain. This was particularly so for the older patients, who probably had had symptoms of the disease for several years. The times were also uncertain with regard to what was defined as initial symptoms in a disease such as this with a widely varied pattern. The symptoms, which were interpreted in this study to be the earliest manifestations of the disease, are given in Table I.

It was thought feasible that the information might be somewhat more certain for the patients who were diagnosed ante mortem. These 49 cases were analysed separately as regards age, when the symptoms began. The results are shown in Table IV. No difference was discovered from the data already given.

In comparing probands and secondary cases within the group of familial cases, there was no significant difference as regards age of onset.

Neither was there any significant difference in age of onset between the patients with pronounced diarrhoea and those without that disturbance (see below regarding the development of the disease).

Pathology

The diagnosis of amyloidosis is in principle dependent on the histopathological examination and the evidence of amyloid deposition in various tissues.

A detailed investigation of 4 autopsy cases was performed. This material was supplemented by autopsy material from another two cases. All six cases were familial. The result was reported separately (VIII).

It is of interest to note that in these cases of amyloidosis there were no macroscopic organic changes which indicated the disease.
Liver and spleen were not enlarged. Their parenchyma had no wax-like or lardaceous character.

When examined microscopically, however, amyloid deposition was found in various tissues. An abundant and wide-spread deposition of amyloid was found in peripheral nerves. Amyloid was also found in spinal ganglia and nerve roots. There was also wide-spread deposition of the amyloid substance in various parts of the autonomic nervous system. Varying amounts of amyloid were discovered in the meninges. On the other hand the central nervous system itself was essentially unaffected. Some atrophy, for example in the anterior horns in the spinal cord, was found in a few cases.

Amyloid was also often found present in many other organs and tissues. In our investigation there were deposits particularly in the walls of blood vessels. The vessels affected were of various calibre.

Amyloid was also wide-spread in conjunction with smooth muscles and perivascularly in the connective tissue.

In the liver, amyloid was observed only in the vessel walls of the portal triad. Amyloid was found also in the spleen in very small quantities. There it was found only in the walls of arteries of various size and not in the red pulp. No amyloid was seen in the islets of Langerhans in the pancreas. Neither was any significant amount of deposition found in the parenchyma of other endocrine organs. In the kidneys the affection was more varied. Sometimes it was only in lesser quantities in the marrow. In other cases there was abundant deposition, even in the glomerules.

Experiences from autopsy material (VIII) and from biopsy examinations (V) formed the basis for certain conclusions concerning suitable biopsy material for the diagnosis of this form of amyloidosis. This will be discussed more closely under the heading DISCUSSION.

Clinical Manifestations

As was stated in the chapter on Pathology, deposits of amyloid were found in this disease to be very widely spread in the peripheral nerves and also in the autonomic nervous system. This affection explains
the clinical pattern of progressive sensory-motor polyneuropathy and of more or less prominent manifestations, indicating disturbances in the autonomic nervous system.

Other localizations of amyloid deposits e.g. adjacent to smooth muscles, in the walls of blood vessels and interstitially in varying amounts in the parenchyma of various organs, show lesions which give conditions for clinical manifestations of different kinds. Therefore in this disease there are grounds for a polymorphous and very varying symptomatology.

After the report of initial symptoms found in the patients in this study special interest will be given in this chapter to the manifestations from certain organs.

Initial symptoms

As was found in our first patients (II) and as was seen in all the material, Table I, the initial symptoms were usually sensory disturbances in the peripheral nerves. They always began in the lower extremities. Various forms of dysesthesia and paresthesia occurred. Severe ache in the lower legs and brief attacks of shooting pain came initially in some cases. Many patients reported an increased sensitiveness to cold as well as coldness in the feet, as early and very troublesome phenomena.

Symptoms of motility disturbances in the gastrointestinal tract appeared early in some of the patients. This could occur even earlier than symptoms in the legs. Also impotence sometimes appeared early. Disturbance of vision, due to vitreous opacities, was reported as the first symptom in three patients.

Peripheral nerves

Sensory manifestations. Initial symptoms usually consisted of various sensory disturbances, Table I. Various types of pain occurred. Irregular attacks of sharp, shooting and burning pain were often the most troublesome. There could also be a deep, stabbing and more prolonged ache, especially in the muscles of the calf. Some patients complained of muscle pain in the lower legs induced by exercise (II, VII). Paresthesia of varying intensity often occurred, such as prickling, formication and burning.
The impression is gained that these various sensory irritative phenomena were much more pronounced in this disease than usual in most other forms of chronic polyneuropathy, e.g. in diabetes mellitus.

Many patients reported that a pronounced sensitiveness to cold and cold feelings in the feet were early and troublesome phenomena, Table I. As part of polyneuropathy such phenomena are usually regarded as cold paresthesia. When it concerns these patients with amyloidosis they were the subject of a special study (VII). The result is commented on in the following chapter about the cardiovascular system.

In all patients there was evidence of a reduction of sensibility. In clinical examination it was found that the superficial sense of feeling was affected earlier and more noticeably than the deep. It was also found that a certain dissociation occurred. Thus, the sensibility of superficial pain, as well as the feeling for heat, was affected on the whole more than that for light touch and cold. Many patients stated that they could not feel the difference between hot and cold bath water with their feet. The senses of vibration and of position were least affected. It is of importance to be aware of this dissociation at the clinical examination of patients with suspected disease at an early stage.

The upper extremities were affected later. In these there was usually somewhat less intensity in the sensory irritative phenomena.

The sensory defects had usually a typical, symmetrical "glove-and-stocking" distribution. They progressed successively in proximal direction. In advanced stages there was a complete loss of sensibility affecting all qualities.

The reduced feeling for heat and pain was of importance for the origin of such complications as burns and scalds which could arise in connection with hot baths and attempts to heat the extremities locally.

**Motor manifestations.** The affection of the motor neurons probably occurs as early as that of the sensory. Initially, however, they are not noticed in the same way by the patient. Atrophy and weakness of the short toe extensors were found to be an early motor manifestation in these patients (II, III). Muscular atrophy and
flaccid paralysis progressed symmetrically in proximal direction. The gait became wide and stumbling. A typical steppage gait with foot-drop developed. In advanced stages total paralysis occurred distally in all limbs, and pronounced weakness proximally, also in the muscles of the trunk.

At a later stage of the disease there were often fixed deformities in the distal joints of the extremities. Among other things flexion-contraction in the finger joints was an example of this.

It can be seen from Table I that abnormal muscular fasciculations appeared quite often. This phenomenon occurred both in the muscles of the extremities and in the musculature of the tongue.

The tendon reflexes became weak successively. It was found at clinical examination that particularly the ankle jerk was changed at an early stage. The tendon reflexes of both upper and lower limbs were lost completely at a more advanced stage of the disease.

Neurophysiological examination. Electromyography (EMG) and estimation of the motor conduction velocity (MCV) of peripheral nerves were performed in 34 patients, Table I. The findings confirmed the clinical diagnosis of polyneuropathy. The results of the neurophysiological examinations of several patients were accounted for separately (III). EMG revealed fibrillations and denervation potentials. At voluntary muscular contraction there were abnormal action potentials. They could be polyphasic potentials with increased amplitude and duration. At maximal contraction a reduced number of motor units were activated.

The MCV was often pathologically prolonged. It was observed, however, that MCV was less well correlated to the clinical pattern than EMG. This can probably be explained by the fact that some efferent fibres with normal conduction velocity can be intact for quite a long time. - Axonal degeneration is reported to be the predominant form of myelinated fibre degeneration in this type of amyloidosis (II).

According to experiences of the investigation (III) MCV does not seem to reveal aberrations as early as EMG does in this
form of amyloidosis. The conclusion was formed that EMG in the musculature of the short toe extensors is a suitable form of examination in the early stage of the disease in order to confirm the clinical suspicion of neuropathy.

In order to refine the diagnostics and to show the damage of efferent fibres the single fibre EMG (40) might be a more sensitive method. Estimation of the sensory conduction velocity can probably also contribute to objectivising earlier the affection of the nerves. These methods, however, were not available at the time for this examination.

In one patient, with slight signs of polyneuropathy and with verified amyloidosis (no. 16), the pattern was complicated by the patient having also progressive muscular dystrophy. This disease occurred hereditarily too in some members of her family. The feature of myopathy predominated at the neurophysiological examination, and the patient was classified as having myopathy.

**Autonomic nervous system.** Various manifestations which arose in these patients pointed to widespread affection of the autonomic nervous system as well. From the clinical point of view, however, it was often not possible to differentiate the disturbances of these from those where local affection of other tissues, e.g. blood vessels and smooth muscles, also occurred. Various disturbances, in which autonomic neuropathy was presumed to contribute to the manifestations observed, are therefore discussed in connection with the respective organs.

**Histopathological examination.** Microscopical examination with regard to the nervous system revealed abundant and widespread amyloid deposition in the peripheral nerves (VIII). Amyloid was also found in the spinal ganglia and in the nerve roots. There was widespread involvement of various parts of the autonomic nervous system as well. On the other hand there was no deposition in the central nervous system itself.

The abundant and widespread infiltration of amyloid substance in different parts of the peripheral nervous system affects probably, by direct local effect, the function of the neurons. It therefore contributes to the various clinical manifestations. However, as etiology and pathogenesis for the development of amyloidosis
are as yet not known, it can not be excluded that also other factors might be of importance, e.g. other structural and/or metabolic aberrations. This question must so far be left open.

Gastrointestinal tract

Symptoms from the gastrointestinal tract occurred at different times and with varying intensity in these patients.

Motility disturbances. In most patients motility disturbances of varying degree appeared sooner or later in the course of the disease. At first there was often a tendency to constipation, which could be very trying. Later there was constipation alternating with diarrhoea. Periods of several days of constipation, accompanied by meteorism, distension, nausea and general discomfort, were followed by periods of frequent emptying of the bowels. This was often explosive diarrhoea with nasty-smelling, gassy feces. This diarrhoea, however, was also accompanied by a general feeling of relief and, to some extent, by a feeling of well-being in comparison to the periods of severe constipation.

Marked diarrhoea occurred in 21 of the 60 patients, Table I. In some cases severe and continuous diarrhoea developed. At the same time there was a rectal incontinence. This made life very difficult for these patients.

Motility disturbance also affected the stomach. It was discovered both by X-ray examination and by gastroscopy (14) that there was often reduced peristalsis and considerably prolonged emptying of the stomach. This disturbance contributed to the symptomatology.

Malabsorption. At the examination concerning malabsorption, steatorrhoea (fat in feces ≥ 6 g/24 hours) was discovered in 7 of the 12 cases examined. Low values of folic acid in serum was found in 2 of 10 patients, low border line values in 5 of 10 patients. Decreased values of xylose in urine at peroral D-xylose test were found in 8 out of 12 patients examined (II). The low values of xylose may reflect a real resorption defect localized to the intestinal wall. It may be pointed out, however, that neurogenic disorder in the digestive canal may influence the peroral
resorption test. It is clear, however, that a great number of these patients have malabsorption.

The occurrence of steatorrhoea in this disease seems not to have been reported previously. Studies based on further patient material have shown steatorrhoea to occur almost to the same extent (14).

Those patients, who had during the course of the disease experienced an early occurring and marked diarrhoea, died sooner than those who had no diarrhoea. This fact is discussed further under the heading of Development of the disease.

Pathology. Histopathological examination showed amyloid deposition in various parts of the gastrointestinal tract (VIII). Amyloid was found accumulated particularly in the muscular layer of the mucosa and in the vessel walls in the submucosa. Amyloid was also discovered in the nerves of the digestive tract. It was not found, however, in significant amounts in the region of the intrinsic plexa of the intestinal wall.

The disturbed motility of the gastrointestinal tract could possibly be due to the amyloid infiltration that was found both in the nerves and in the smooth musculature. Also the absorption capacity is probably affected by the amyloid deposition in various structures of the wall of the intestine.

Preliminary examination with ordinary light microscope of biopsy specimens from patients with steatorrhoea, showed no significant atrophic changes of the intestinal villi. Later studies have verified these findings (15).

Peptic ulcer. To what extent this amyloid disease with neuropathy is connected with the occurrence of peptic ulcers of the stomach and duodenum was not penetrated more closely in this study. It is, however, of interest to note that several patients had peptic ulcer and gastroduodenitis verified by X-ray, Table I. This often seemed to have been present before symptoms of peripheral neuropathy appeared in the extremities.

Genitourinary organs

Amyloid infiltration was found with widespread occurrence in the
nerves of the genital organs, both in men and women (IV, VIII). In men the affection of these nerves was interpreted to be the cause of impotence. This disturbance was often present, even in the early stage of the disease (II, IV). To what extent the affection of the nerves of the female genital organs influenced their function was not examined in this study.

Urinary bladder. Disturbance of the function of the urinary bladder was found to be frequent. It was analysed more closely (IV, VI). To summarise it can be said that this disease often develops with the following disturbances or tendency to them:

1. Reduced bladder sensibility.
2. Disappearance or decreasing of the contraction capacity of the detrusor musculature.
3. Increased rigidity of the bladder wall.
4. Increased bladder capacity.
5. Overflow incontinence.
6. Retention of urine with risk for urinary tract infection.

Histopathologically, amyloid was found in the vessel walls, nerves and smooth musculature of the wall of the urinary bladder (IV). It is probable that these various localisations of amyloid deposition cooperate to cause the disturbances that were found.

Kidneys. Histopathological examination of 9 autopsy cases revealed very variable amounts of amyloid accumulation in the kidneys (IV). Deposits were found in the vessel walls in the cortex in 7 cases. Four of these had also glomerular lesions which were pronounced in two. This varying affection of the kidneys had variable clinical correlations too. Thus, increased value of creatinine in serum was observed only in 5 of 26 patients examined (IV). The creatinine was normal in several patients with symptoms of the disease for ten years or more.

Proteinuria was found in 14 of 28 patients examined (IV). In 10 of them bacteriuri and pyuria were also found. Histopathologically, there was the typical picture of chronic pyelonephritis in 2 of the 9 cases examined.

Serious kidney insufficiency because of amyloid deposition and/or pyelonephritis was seldom present in these patients. Only in
4 of 27 deceased patients was uremia a contributory cause of death, Table II. Nephrotic syndrome was confirmed in only one patient (IV).

**Cardiovascular system**

Both the heart and blood vessels of various calibres, arteries and veins, were found to be the seat of amyloid deposition as was the nerves of various parts of the cardiovascular system (VIII).

**Heart.** Various manifestations indicating affection of the heart were established (II). It was conduction and rhythm disturbances that were most prominent. Heart enlargement and failure were found more seldom.

It is, of course, difficult to determine to what extent other heart affection, particularly cardiosclerosis, contributed to the dysfunctions clinically observed as the patients mostly belonged to a relatively high age group. However, when autopsy material was studied, an amyloid deposition was often found to such a degree that the function of the myocardium might have been affected (VIII). Furthermore, amyloid was found in connection with the Purkinje fibres. This localization of amyloid might contribute to the occurrence of the conduction and rhythm disturbances that were observed.

Complete A - V block was found in 3 patients, Table I. These patients received treatment by a pace-maker.

**Blood pressure.** A low blood pressure was found in most patients, Table I. It should be noted that most of these patients were of a relatively advanced age. Blood pressure of 19 of the 50 patients examined was below 130/80 mm Hg. A marked disposition to orthostatic hypotension was found in 10 of them, Table I. Most of these had no, or only very slight, increase of the pulse rate in connection with the fall of blood pressure when standing. A disposition to syncope was found in some of them.

The pathophysiological cause for low blood pressure and orthostatic hypotension was not analysed. It seems to be likely, however, that the widespread amyloid involvement of the autonomic nervous system might be of importance.
Peripheral circulation. Investigation of peripheral circulation was performed. The results were reported separately (VII).

As patients with amyloidosis and polyneuropathy often have signs and symptoms of circulatory disturbances in the extremities, especially the legs, such patients and controls were examined with oscilometry and digital pulse plethysmography in order to estimate the occurrence of possible arterial circulatory insufficiency. No signs of significant obliterative arterial changes were found.

Determination of skin temperature in fingers and toes during body-cooling and at subsequent indirect heating was also performed. At low environmental temperature the skin temperature was higher in patients than in controls. In some patients there was nearly no decrease of skin temperature, despite a long period of cooling and a low rectal temperature. At indirect heating a marked increase occurred in the skin temperature of the toes and fingers of the controls. In most patients this reaction was completely absent in the toes. The reaction was absent or reduced in the fingers of most patients as well. These deviations can be explained by nerve damage caused by amyloid deposition in the nerves. Amyloid deposits in the walls of small blood vessels may be an additional factor.

It is suggested that the increased cold-sensitivity often experienced by the patients, (see above concerning initial symptoms and sensory manifestations), is the result of the abnormal peripheral vascular response in the skin.

Maximum blood flow in the anterior tibial muscle after combined ischemia and exercise, investigated with radioactive xenon, was reduced in half of the patients examined (VII). Thus, the blood supply of the skeletal musculature can be compromised, too, in these patients. This is probably a contributory cause of the muscular discomfort experienced by some patients during and after exertion (II).

Eyes

The occurrence of vitreous opacities was of great importance concerning the decision of diagnosis in our first patients (I).

In the material at hand vitreous opacities were revealed in 9 patients, Table I. No opacities occurred in 9 other patients. The other 42 cases were not adequately examined ophthalmologically in this respect.
This affection of the vitreous body can be an early phenomenon of the disease. It was in fact reported as the initial symptom by 3 patients (no. 2, 3 and 50), Table I.

The opacities in the vitreous body had a characteristic appearance with an amorphous, white material in irregular, "glass-wool"-like formations (I). They were often localized in the anterior part but also in the posterior part near the retina. In advanced stages the opacities involved almost the whole vitreous body. Vision was affected depending on the amount of deposition in varying degrees, from floating dark patches and bands to total blindness (I).

Anisocoria and irregular pupils with slow reflexes were also observed. In 2 patients (no. 7 and 54) typical Argyll-Robertson pupils with miosis were found. Serological tests of luetic infection were negative in both cases.

Histopathological examination of autopsy material revealed that the vitreous opacities had the characteristics of the amyloid substance (VIII). Amyloid infiltration was also observed in the vessel walls of the sclera, chorioidea and retina. Deposits were also found in vessel walls and in nerves around the globe of the eye. On the other hand, there was no amyloid found in the optic nerve itself.

**Larynx**

Several patients had various degrees of hoarseness. This was obvious in 20 cases, Table I. Seven patients had no hoarseness, while it was difficult to judge in the rest of the cases. Seven of the patients with marked hoarseness (no. 2, 6, 7, 9, 10, 11 and 24) were examined by an otorhino-laryngologist. No local changes of the vocal chords or of the larynx otherwise were found. Nor could any paresis or function disturbance of the vocal chords be discovered by routine examination. Investigation with stroboscopic light, however, was not performed.

Histopathological examination of autopsy material revealed amyloid deposits in the nerves as well as in the muscles of the vocal chords (VIII). These changes can explain the disturbed function of the chords.

It can be mentioned here that patient no. 2 during her final years had difficulty with her breathing which had the character of stridor. Patient no. 6 had repeated attacks of difficult breathing.
They were described as attacks resembling suffocation. Another person, belonging to family 2, but not included in this material, died from an attack of suffocation. He had been interpreted earlier at a medical examination as suffering from bulbar palsy. He was said, however, also to have had manifestations consistent with polyneuropathy. Histopathological examination was not performed.

**Skin**

Various changes of the skin were found in these patients. This, however, did not become the object for detailed study. Generally it can be said that in many patients their skin was dry, thin and "lifeless", especially distally in the limbs. This was interpreted to be trophic changes. The small chronic ulcerations, which appeared on the toe and finger pads (no. 4, 21, 36 and 44) were also regarded as such.

Skin changes similar to acquired epidermolysis bullosa occurred in some patients (no. 29, 46 and 55), Table I. These changes were localized mostly on the lower legs.

Two patients (no. 26 and 51) had relapsing eruptions of urticarial rash, particularly on the trunk.

Moreover, changes similar to dermopathy diabetica (25) and other lesions similar to those in elderly diabetics were observed. This was studied in greater detail (21, 22). It was found to occur in most of the patients examined.

**Other manifestations**

Some other manifestations were observed, among others from the skeleton and joints.

Patient no. 49 had pain and some swelling on the front of his left foot for a year or two. X-ray examination revealed partial destruction of the head of the third metatarsal bone and also slight destruction of the base of the corresponding basal phalanx. Histopathological examination of biopsy from this part showed only slight unspecific inflammation. No amyloid deposition was observed.

Three patients had arthropathy and joint deformations of the type of Charcot joints. Patient no. 11 had repeated episodes of painless distortion of both ankles, which required active reposition.
Patient no. 23 had a tendency to distortion and swelling of the ankles as well as instability and deformation in both knee joints. She also contracted fractures on the medial condyle of the tibia in both knees. These injuries were free of pain. Patient no. 44 had instability and hyperextension and painless distortions of both knee joints. Roentgenogram showed greatly reduced cartilage and big osteophytes.

**Loss of weight**

As can be seen on Table I, there was a great loss of weight in many patients. This reduction of weight usually took place in a relatively short time, 1 - 3 years. Anamnestically speaking, this could not often be directly correlated with any marked diarrhoea. The phenomenon, however, might mainly be connected with malabsorption, diarrhoea tendency and constipation. Atrophy of skeletal musculature which sometimes progressed quite quickly could also be of importance in this respect.

**Laboratory tests**

*Sedimentation rate.* The sedimentation rate was normal in the majority of patients. A slight rise was found in a few cases at the time of the examination. The increase might be correlated with secondary changes, e.g. kidney affection with a nephrotic syndrome (no. 11), and skin lesions with secondary infections (no. 29 and 46).

The disease amyloidosis itself did not seem to be accompanied by any rise of the sedimentation rate.

*Hemoglobin.* The hemoglobin value was normal in practically all cases.

*Protein analysis.* Paper electrophoresis was carried out for serum protein in 35 cases. Slight aberrations were observed in a few cases. These were unspecific changes of uncertain importance. In none of the cases examined was there discovered any M-component.

A quantitative serum immunoglobulin analysis was performed in 4 patients (no. 9, 22, 26 and 51). No abnormality was discovered in these cases.

In a particular study concerning disturbances of the genitourinary
organs, proteinuria was found in 14 out of the 28 cases examined (IV). Electrophoresis of the urine was performed in 4 cases (no. 10, 14, 22 and 34). No Bence Jones protein was shown in these cases.

Lumbar liquor. Examination of the cerebrospinal liquor after lumbar puncture was carried out in 24 patients. No pleocytosis was present in any case. The content of protein was varying. In one case (no. 45) it was found 185 mg/100 ml. As for the rest, values between 16 and 83 mg/100 ml were found, mean 50 mg/100 ml. There was a concentration of over 50 mg/100 ml in 9 patients. Electrophoresis on liquor protein was carried out in 16 cases. No remarkable changes were observed.

Diagnosis

Although various clinical manifestations, especially in the case of familial occurrence, very definitely can point to the actual disease, histopathological verification is necessary to confirm the diagnosis of amyloidosis.

In this type of amyloidosis, skin and rectal biopsy were found to be valuable methods (V). It was found important that the biopsy material was representative. In skin biopsy amyloid deposits were found especially in blood vessel walls, in arrector pili muscles and adjacent to sweat glands. These structures should therefore be included in the biopsy material. Biopsy from the rectal mucosa must include the muscular layer to be adequate. The submucosa with its blood vessels ought also to be included in the material.

Biopsy of peripheral nerves, e.g. the sural nerve, was found to be a valuable alternative or complement (V).

At the examination of autopsy material no, or only very little, amyloid was found in the liver and spleen in several cases (VIII). These organs are therefore judged unsuitable for diagnostic biopsy examination of this disease.

The degree of amyloid accumulation in the kidneys was found to be very varying. Biopsy from this organ might be of value in certain cases.

As amyloid deposition in the tissues sometimes can be only
minimal, the histopathological examination of biopsy specimens must be carried out thoroughly. At routine examination staining should be done with alkaline Congo red and the examination performed in polarised light (V). With ordinary light microscopy the amyloid appears faintly red. In polarised light it shows the characteristic bright yellow-green colour.

It can be difficult to receive at all times representative biopsy material. This is perhaps particularly the case in the early stages of the disease. In a clinically suspected case repeated and complementary biopsy specimens must be taken. According to experiences from the investigation of these patients in northern Sweden, biopsies from the skin, rectum and the sural nerve can be recommended.

As can be seen from above, this form of amyloidosis has a very variegated pattern. It seems, therefore, to be of importance to differential diagnosis in many various situations, not only in polyneuropathy. The varying pattern of symptoms explains the different inadequate diagnoses, which had been given beforehand about the patients in this study. Some of these diagnoses are given in Table II.

Regarding the five patients in group 3 in this account (see Material), the diagnosis of amyloidosis had not been established by histopathological evidence. The diagnosis in these cases was based partly on the clinical manifestations, partly on the hereditary conditions. These conditions will be discussed under the heading Genetics.

Development of the Disease

The time interval from the initial symptoms to the diagnosis for the 49 cases, which were diagnosed ante mortem, can be seen in Table II. The interval mentioned was 1 - 8 years, median 5 years, mean $6 \pm 4.0$ (S.D.) years. There was no difference in this respect between men and women.

Twentyseven of the 60 patients have died. Immediate causes of death as well as age at death have been given in Table II. For all deceased patients the age at death was found to be as follows: median age 66 years, mean age 65.6 $\pm$ 9.9 (S.D.). There was no significant difference between men and women.
The duration from the initial symptoms till death is also given in Table II. This information is summarised in Table VI. For the whole group the median was found to be 9 years and the mean $10.7 \pm 6.1$ (S.D.) years. For 20 men the median interval was 9 years, mean $11.3 \pm 6.9$. Seven women had a median of 8 years and a mean of $8.7 \pm 2.7$ years. There was no significant difference between men and women in this respect either.

For the 27 patients who died, 12 of them (no. 9-14, 21, 22, 33, 34, 43 and 47) had very pronounced gastrointestinal symptoms with diarrhoea early on in the development of the disease, Tables I and II. The age at death for these 12 patients is summarised in Table V. Median age was found to be 61 and mean age $61.1 \pm 7.4$ (S.D.). As can be seen from Table VI the median for the interval between initial symptoms and death was 7.5 years and the mean was $7.3 \pm 2.0$ (S.D.) years.

For the other deceased patients, those who had no early, pronounced diarrhoea, 15 cases (Tables I and II), the information about age at death is summarised in Table V. The median was 68 years, and the mean age was $69.2 \pm 10.3$ (S.D.) years. The time interval from the initial symptoms till death for these 15 patients was according to Table VI: median 12 years and mean $13.4 \pm 7.0$ years.

The difference between these two groups of patients - those who had pronounced diarrhoea and those who did not have this - as regards age of death, mean age $61.1 \pm 7.4$ respectively $69.2 \pm 10.3$, is significant ($0.05 > p > 0.01$). As regards the time interval from the initial symptoms till death, the difference - mean $7.3 \pm 2.0$ years respectively $13.4 \pm 7.0$ years - is also significant ($0.05 > p > 0.01$).

**Incapacity for work**

This disease showed generally a successively progressive development. It was mostly the polyneuropathy, but also the gastrointestinal disturbances with diarrhoea and malabsorption, that resulted in increasing invalidity and incapacity for work. From Table II it can be seen that 32 of these 60 patients, 22 men and 10 women, became completely unable to work before the age of 65 years.

It can be seen, too, from Table II, that many patients needed
continuous care. This was usually carried out in the home. However, besides this, it was necessary with repeated periods of treatment in hospital. Some patients were cared for continuously in institutions for the chronic sick.

Treatment

In amyloidosis secondary to chronic inflammation, the development of the amyloid disease has been observed to be influenced favourably when measures have been taken against the underlying disease (23, 42). Otherwise there is at the present time no known efficacious treatment for amyloidosis. One has to turn to supportive and symptomatic measures.

It is important to treat supervening infections, e.g. infection of the urinary tract, in these patients.

To patients with diarrhoea it is often difficult to give effective treatment against this disturbance. Both malabsorption and malnutrition often arise. This can be influenced to a certain extent in different ways. Treatment with a special diet, consisting of easily digested food substances, has in some cases resulted in a noticeable improvement with weight increase and improved well-being (14).

The importance of adequate treatment of the skin lesions appearing in the lower limbs has been emphasized (22).

Geographic Distribution

Birthplaces for the 42 familial and for the 18 sporadic cases are shown on the map, Figure 16. Two distribution areas were found.

1. The inland area. Twelve familial cases, belonging to families 1, 5 and 7, were born in the inland, Lappland. The members of families 5 and 7 had, most probably, the same forefathers as family 1. These forefathers were Finnish immigrants who came to the area from the south-east in the 17th century (12). This was also the case with the sporadic case in the inland area and with 2 of the
sporadic cases in the intermediary zone between the inland and the coastal area.

2. The coastal area. Most of the diagnosed cases were born in the coastal area and in the country nearest to the coast of the province of Västerbotten and Norrbotten.

GENETICS

Background

The mode of inheritance in the Portuguese type of familial amyloidosis with polyneuropathy has been the subject of two investigations. Becker et al. computed the actual morbidity risk for the sibships of the patients to be about 40% (6). Andrade et al. analysed a numerically more important material distributed over 148 sibships (3). According to the maximum-likelihood-method, and assuming a complete selection, they found the proportion affected per sibship to be 30.8% with a standard deviation of 2.3%. Assuming a single selection, the figures were 21.3% and 1.9% respectively. The results of the analysis of these two materials, together with the pedigrees presented, were considered to be in agreement with an autosomal dominant mode of inheritance.

The patients, who were included in Table I, and who were the basis for the above account, had undoubtedly polyneuropathy. Amyloid deposition was determined in 55 of the 60 cases. As was stated before, histopathological examination was not performed on the other 5 cases (see MATERIAL). Preliminary pedigrees of 2 families with some of these patients were reported previously (II).

At an attempt to perform more detailed genetic analysis, various difficulties arose depending on the necessity of diagnostic certainty. With a disease such as this, it is not always possible to make a clear distinction between a sick and a healthy individual. In connection with the examination of relations of the affected patients, there occurred sometimes anamnestically slight symptoms which could be an expression of incipient illness, but which could not be verified at clinical examination. It could not be excluded that the disease in
some cases had a very slow progression with only slight symptoms. Sometimes the affection might have remained subclinical. Thus, to ascertain the diagnosis in the early stages was not always possible in a disease such as this with an often insidious development and with such a varying symptomatology. The technical aids which were at hand, e.g. for examination concerning neuropathy (electromyography and estimation of motor conduction velocity), did not always seem to give a sufficiently decisive result for an early diagnosis.

Another difficulty in diagnosing this disease, concerned the problem of revealing amyloid deposits in clinically suspected cases by histopathological examination. It is probably so, that small biopsy specimens are not always enough to reveal amyloid. The question if the disease can develop without the appearance of amyloid deposits demonstrable by the histopathological techniques used, is discussed further on.

No biochemical abnormalities of diagnostic significance, e.g. in the blood or urine, were known at the time of this investigation.

According to the account of material, it was established that amyloidosis was histopathologically confirmed for group 1 and 2. Regarding group 3, clinical manifestations occurred in agreement with those cases which were verified histopathologically. The five patients in group 3, however, were deceased, and there was no tissue material available for histological examination. Genealogically they belonged to families 1, 2 or 10, and they were close relations (brothers, sisters or parents) to patients in group 1. The diagnosis was therefore based both on clinical and genealogical conditions.

It is remarkable that in families 1 and 2, several patients were observed to have distinct clinical manifestations as seen in familial amyloidosis with polyneuropathy, but in whom amyloid deposits were not found in biopsy examination. These patients are accounted for in the pedigrees, Figure 1 and 2, and in Table VII and VIII. The polyneuropathy in the extremities was graded in three degrees: +, ++ and +++ (III). From Table VIII it can be seen that regarding the 49 cases where amyloid deposition was shown by biopsy examination, the neuropathy in the legs in 8 cases belonged to grade +, in 15 to grade ++ and in 26 cases to grade ++++. Thus, it was often possible to prove amyloid in those patients classified in
grade + and ++. Of those patients who are accounted for in Table VII, no less than 6 had polyneuropathy in the lower extremities of grade ++ and grade ++++. Despite this, amyloid deposits could not be shown in examination of biopsy specimens.

Thus, it seemed that even in patients with marked signs and symptoms it was not always possible to establish amyloidosis by biopsy examination. It was remarkable that it was not possible to prove amyloid depositions in autopsy material from patient 1:IX: 26, Table VII and Figure 1. Particularly the latter circumstance brought into question how much the clinical manifestations in these patients really depend on the amyloid deposits which could be shown by the histopathological technique used.

**Genealogical Studies**

**Pedigree 1 (Figure 1)**

Several patients living or born in Lappland could be connected to one big family. The pedigree over the family is shown in Figure 1. Most of the patients in that family belonged to different sibships in one and the same generation (generation IX). All their respective parents were deceased before this examination. There was no information that any parent had manifestations of the disease. However, there was a dependable report that the subject VII:11 became both "lame and blind".

It was established that the family had its origin from Finnish immigrants, who came as colonists to Lappland in the 17th century (12). The earliest known forefathers in generation I lived in a very confined area in the south-eastern part of Lappland. They were most probably related to each other (13).

As stated above, it was of great interest to note that further cases of neuropathy, which was unmistakable clinically and neurophysiologically, but without demonstrable amyloidosis, were diagnosed in this family. This fact was preliminarily announced previously (II). The cases are presented in Table VII and VIII. They are also taken up in the pedigree of this family, Figure 1.
Pedigree 2 (Figure 2)

The proband in this family was case no. 9 (IV:74, B:1 in earlier publications). Information was received that a brother had similar symptoms and that a deceased cousin had had polyneuropathy. Several members of the family were examined. A pedigree was drawn up (Figure 2). This family was traced back genealogically, partly as far as to the 16th century. No certain connection to family 1 could be proved. Neither could any connection to Finnish immigrants be reliably established.

In this family, too, there were patients with clinical manifestations such as are found in familial amyloidosis with polyneuropathy, but in whom no amyloid deposits could be seen at biopsy examinations. They are accounted for in Table VII and VIII and are shown in the pedigree, Figure 2. When clinically examined, most of these cases had only slight manifestations, which could represent an early stage of neuropathy. Two of them (case IV:38 and IV:47) had, however, clear and undoubttable polyneuropathy.

Pedigree 3 - 15 (Figure 3 - 15)

In 24 further cases (clinical no. 19 - 42) there was proved, or probable, familial occurrence of the disease. These patients belonged to 13 smaller families (Figure 3 - 15). Some of them were traced several generations back genealogically. No definite connection with families 1 and 2 could be shown. It can be noted, however, that birthplaces for many of these patients or their close forefathers were, from a geographical point of view, in the same area as those of family 1 or family 2.

Sporadic cases

Eighteen cases were regarded as sporadic. According to information from the patients themselves no similar symptoms of the disease existed in their parents or in their brothers, sisters or children. Examination of their relatives, however, was not performed.

Clinically and histopathologically, no difference could be shown compared with the familial cases accounted for above. It was not possible to decide whether these cases were genetically of the same nature as the familial.
The data compiled by the genealogical studies were analysed statistically. Taking the diagnostic problems into consideration, which were accounted for above, calculations were carried out concerning the proportion affected in sibships on the basis of material from pedigrees 1 - 8 and 10 - 14 (see Figure 1 - 8 and 10 - 14 and Table X). Because of incomplete information concerning sibships in families 9 and 15 (Figure 9 and 15) these were not included in the calculations.

The following persons were regarded as being affected:
1. Patients examined and shown to have definite and unmistakable polyneuropathy (solid symbols).
2. Patients who at the clinical examination had symptoms and/or signs indicative of polyneuropathy (half-filled symbols).
3. Patients who were reliably reported by their relations to have had unmistakable signs and symptoms of polyneuropathy (symbols with lines).

Those sibships were included in the statistical calculations, in which at least one sib was affected and at least one had been examined. Also those cases were included in the calculations where histopathological examination of biopsy and/or autopsy material had been unable to prove amyloid deposits.

The description, "normal sibs", was based partly on the result of clinical examination, partly on information from other sibs. Also sibs who had died before this study was performed were included. Considering the results accounted for above, concerning age at onset of symptoms, those sibs were not included who had died before reaching the age of 25.

The composition of the material can be seen from the pedigrees, Figure 1 - 8 and 10 - 14 as well as Table IX - X.

The proportion of affected sibs within the sibships was estimated according to the maximum-likelihood-method (31). The calculation was performed 1) assuming complete selection (complete ascertainment) and 2) assuming single selection (single ascertainment). The selection is said to be complete, when each affected individual is discovered because he or she is affected and not because of the discovery of the abnormality in a sibling (31).
Assuming complete selection, the proportion affected was found to be 26.1% with a standard deviation of ± 3.37. Assuming a single selection, the corresponding figures were 17.9% ± 2.97. Considering the mode of procedure for gathering this material, the value of complete selection should be the most appropriate.

The figures obtained were somewhat lower than those given by previous authors, with regard to the Portuguese type of amyloidosis with polyneuropathy (3, 6). The difference might depend on the higher age at onset of illness among the Swedish patients. With regard to the possibility of reduced penetrance and higher age at onset, the figures are consistent with the assumption of autosomal dominant mode of inheritance.

The figures per se do not exclude the possibility of recessive inheritance. This alternative, however, must be rejected although particularly pedigree 1 shows a high frequency of consanguineous marriages. In all cases, namely, where parents could be examined, one of the parents had the defect. Furthermore, the proportion affected sibs was not higher in the 15 families which had an affected parent than in the 26 families where the disease did not occur in either of the parents. (The last named parents were not examined. According to information given by their children no manifestations of the disease had appeared). Approximate calculation according to Li and Mantel (cf. 20) gives the figures 26.1% and 25.9%, respectively, for these two groups. The consistency of these figures agrees with dominant mode of inheritance. With a recessive mode of inheritance, the proportion affected within sibships would be greater if one or other of the parents had the disease, than if neither of the parents had the disease (50% and 25%, respectively).

The results of the analysis of family data together with the presented pedigrees are thus consistent with the assumption of an autosomal dominant mode of inheritance. Although the material for analysis was incompletely examined, the results indicate a reduced penetrance. As it was stated above, the age of onset of the disease was very varying. From the survey concerning the clinical material, it was evident that there existed very variable expressivity in various respects. Different kinds and intensity of the manifestations, as well as very varying development of the disease, are examples of the variable expressivity.
The expressivity was found to be not only individually different. Also interfamilial differences were shown. Thus the affection of the digestive system with troublesome diarrhoea was seen to be more predominant in certain families (family 2, 4 and 10) than in other families. This condition was of importance in the development of the illness. This was more serious for the patients in family 2 than for those in family 1. The time interval from the beginning of symptoms till death can be seen on Table II. For six deceased patients in family 2 it was 8.2 ± 1.8 (S.D.) years. For the six deceased patients in family 1 the interval was 19.5 ± 6.7 years. The difference is statistically significant (0.01 > p > 0.001).

The variable expressivity of the disease has not been particularly emphasized before. As far as is known, interfamilial differences concerning clinical manifestations have not been reported previously.

DISCUSSION

Various heredofamilial syndromes of amyloidosis have been described during the last years (cf. 10, 24). In some of them polyneuropathy is an always occurring manifestation, more or less pronounced. This has been the reason why it has been confined as a particular clinical entity. The familial amyloidosis with polyneuropathy has been, in its turn, divided into three types (4):

1. The Portuguese type (1, 36);
2. The Indiana-Maryland type (24, 35);
3. The Iowa type (41).

The characteristic in type 1 and 3 is that the neuropathy begins in the legs. Type 2 has neuropathic manifestations mainly in the upper extremities, most often as a carpal-tunnel-syndrome. Type 3 is reported to have a high frequency of nephropathy with uremia as well as peptic ulcer.

A different type of hereditary amyloidosis with nervous involvement has been reported from Finland (26). Most characteristic for this disease is lattice dystrophy of the cornea and paralysis of the facial nerves.
In all of the patients diagnosed in northern Sweden the symptoms were first and most pronounced in the lower extremities. It was therefore natural to compare the results of this investigation first and foremost with type 1 and to a certain extent also with type 3.

Clinical aspects

The results of the examinations of the patients in northern Sweden showed, in many respects, agreement with what was reported earlier concerning type 1 especially from Portugal (1, 2, 5, 8, 9, 29 and 34). Certain differences, however, were found.

One difference to earlier reports concerning type 1 was that the age of onset in the Swedish patients was higher. The mean age for onset in the existing material was around 55. From Portugal it was reported that the onset usually occurred between 25 and 35 years of age (4).

Steatorrhoea and other signs of malabsorption were rather common (II). Steatorrhoea was previously not reported from other countries. Whether this difference is real can, however, not be proved.

It is remarkable that peptic ulcer and gastroduodenitis occurred to such a wide extent among the Swedish cases. The impression was gained that the same was valid for their relations, too, particularly in family 2. This fact shows a certain similarity to the cases, which were reported from Iowa, type 3 (41). On the other hand the cases seemed more compatible with the Portuguese as regards kidney affection (5). Serious kidney insufficiency with uremia as found in type 3, occurred only seldom.

In this investigation of patients in northern Sweden, studies were performed more closely of some clinical manifestations of the disease, which were not or only partly taken into consideration by earlier authors. They concerned malabsorption, peripheral polyneuropathy, dysfunction of the urinary bladder and signs indicating disturbance of the peripheral circulation distally in the extremities. The results have been discussed already.
It can be added here that chronic infection of the urinary tract has been regarded as being of etiological importance for the arial of systemic amyloidosis (7). The results of the studies on the Swedish patients showed that amyloidosis with polyneuropathy was accompanied by dysfunction of the urinary bladder. This disturbance brought the risk for infection of the urinary tract. Thus, in this form of amyloidosis, infection of the urinary tract is probably a secondary consequence of polyneuropathy and not an etiological factor for amyloidosis.

Histopathological aspects

As regards the histopathological findings, the observations made in this material agreed in most respects with those reported from Portugal (36, 38 and 39). It can, however, be noted that no significant amyloid deposition was found in these cases in the area of Auerbach's plexus in the intestinal wall. Such a deposition has been stated to exist in a marked degree in the Portuguese cases (37). Whether this difference is real, must, however, be left as an open question.

With regard to the diagnostic methods for proving the presence of amyloid infiltration, skin biopsy was considered to be a valuable method. This is also in agreement with the Portuguese findings (39).

Rectal biopsy is regarded as being a suitable method to diagnose systemic amyloidosis (16, 27). This method has not been more closely discussed earlier in this form of amyloidosis. The result of examinations of the present material showed that rectal biopsy was a valuable alternative or complement in this disease, too.

Parenchymatous organs were regarded as the most suitable for diagnostic biopsy procedure in type 3 (41). This is in contrast to the experience with patients in northern Sweden. Only minimal amyloid deposits were found in the liver. In many autopsy cases, only very slight or no deposition at all was found in the spleen. These findings are in agreement with those from Portugal (36). They show that biopsy from the liver or spleen is not to be recommended in diagnosis.
Etiological aspects

According to the statements given above, genetic factor is of etiological importance. The possibility of other etiological factors, however, should be taken into consideration. Although the clinical pattern and the histopathological changes are mainly the same, some interfamilial differences, as well as the appearance of sporadic cases, may indicate heterogeneity. The possible importance of environmental factors on the development of this form of amyloidosis is quite unknown.

SUMMARY

Sixty patients with amyloidosis and polyneuropathy were studied. The patients were born and lived in the north of Sweden. In 55 patients, the diagnosis was confirmed by the finding of amyloid deposits. In 42 patients, the disease was familial. Eighteen cases were classified as sporadic. The disease was observed almost twice as much in men as in women.

The clinical manifestations of the disease, as well as the histopathological changes, were to a great extent in agreement with those previously described from Portugal. Familial amyloidosis with polyneuropathy had not been described previously from the Nordic Countries (Denmark, Finland, Iceland, Norway and Sweden).

The disease is a systemic disease. Histopathological investigation of autopsy material showed that characteristic findings were amyloid deposits in the peripheral nerves, including the autonomic, in spinal ganglia and nerve roots, in the walls of blood vessels of varying calibre, in perivascular connective tissue and adjacent to the smooth muscles. Liver and spleen were involved to a very slight extent. The degree of kidney involvement was varying. Biopsy material from skin, rectum and peripheral nerve was found to be suitable for histopathological proof of amyloid deposition.

The patients had manifestations of the disease from several different organs. Polyneuropathy, which began with various sensory disturbances distally in the lower limbs, was a constant finding. Trouble-
some, irregular attacks of sharp, shooting and burning pain often occurred. A dissociated sensory loss was found with early impairment of pain and thermal sensibilities. An early sign of the polyneuropathy was atrophy of the short toe extensor muscles.

Accounts were made about various clinical manifestations. Attention was paid to the initial symptoms as well. The age of onset varied between 29 and 75 years. The mean age was 53, which was more than 10 years older than that reported from Portugal. The age of onset was the same in men and women.

The time interval between the initial symptoms and diagnosis was about 5 years. Twenty-seven of the 60 patients have died. The duration of the illness varied between 4 and 31 years and was in mean 12 years. The majority of the 60 patients were incapable of work before the age of 60 – 65.

The most predominant clinical manifestations in addition to the neuropathy localised to the extremities, were impotence, disturbances of urinary bladder emptying, constipation, which was later in the development of the disease often followed by diarrhoea, loss of weight, visual disturbance in connection with vitreous opacities, hoarseness, low blood pressure and orthostatic hypotension, cardiac rhythm disturbances as well as symptoms indicating circulatory disturbances distally in the limbs.

Individual variations concerning various manifestations of the disease were obvious. Interfamilial differences regarding clinical manifestations, e.g. gastrointestinal disturbance with diarrhoea occurred also. The time of survival after onset of the disease was shorter in families where the diarrhoea was marked. Steatorrhoea and other signs of malabsorption were often apparent in those patients. Certain other manifestations of the disease were also studied more closely, especially the peripheral polyneuropathy, the disturbed function of the urinary bladder and the symptoms indicating circulatory disturbances distally in the limbs.

Neurophysiological studies, concerning the polyneuropathy in the extremities, showed that electromyography (EMG) as a diagnostic aid was superior to determination of the motor conduction velocity of peripheral nerves. EMG, e.g. of the short toe extensor muscles, was found to be a valuable diagnostic method in the early stage of the disease.
The disturbance of the urinary bladder function was characterised by reduced sensibility of the bladder, disappearance or reduction of the contraction power of the detrusor musculature, often an increased rigidity of the bladder wall, increased bladder capacity, overflow incontinence and urine retention with increased risk for infection of the urinary tract.

In clinical physiological studies concerning the peripheral circulation in the extremities, there was shown no sign of obliterative processes localised to the arteries of the extremities. Arterial angiography, which was performed in a limited number of cases, did not show either any signs of artery obliteration. At body-cooling and subsequent indirect heating it was found, however, disturbances of the vasomotor responses in the skin. The ability of reactive hyperemia in skeletal musculature could be impaired too.

The disease could develop with marked clinical symptoms, e.g. polyneuropathy, without it being possible to prove, with available methods, any deposition of amyloid in the tissues, where such usually appears in these patients.

The predisposition of the disease is in all probability inherited and the mode of inheritance autosomal dominant with incomplete penetrance. That this is the case was supported by the pedigrees presented and by the analysis of the proportion affected sibs within sibships.
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APPENDIX
SURVEY OF CL INICAL DATA

A survey of some clinical data of the 60 cases of amyloidosis with polyneuropathy is given in Table I and II.

Comments to Table I
Column 1. "Clinical numeral" indicates identification number of each case reported in the clinical part of the study. Cases designated with numbers 1 - 42 are familial ones, while cases 43 - 60 are considered as sporadic.

Column 2. "Genetical numeral". The familial cases are designated by numerals referring to Pedigree-Generation-Individual in accordance with the pedigrees in Figure 1 - 15. In order to make possible the identification the designations that were used in previous reports (I - VIII) are also presented here.


Column 4. "Age at onset of symptoms" is given in years according to information given at the time of the examination noted in column 6.

Column 5. "Initial symptoms". The following abbreviations are used: C = coldness of feet; M = hypalgesia and hypesthesia; P = pain in the lower limbs; G = gastrointestinal disturbances; O = opacities of the vitreous body; I = impotence; Ca = cardiac symptoms.

Column 6. "Age at examination" is given in years.

Column 7 and 8. "Peripheral neuropathy" of arms and legs is graded semiquantitatively as described previously (III). + = slight, ++ = moderate and +++ = marked neuropathy.

Column 9. "EMG and MCV". Electromyography (EMG) and motor conduction velocity (MCV) of peripheral nerves confirming the diagnosis of polyneuropathy is indicated by "+", not confirming by "-".

Column 10. "Fasciculations". Spontaneous fasciculations appearing in the musculature of the limbs (L) and tongue (T) are noted. "0" means that no fasciculations were observed at the time of the examination.

Column 11. "Diarrhoea". Daily, frequent and troublesome diarrhoea at the time of the examination is indicated by "+". No or only sporadic tendency to diarrhoea is indicated by "0".

Column 12. Marked weight loss occurring in 1 - 3 years is given by figures (kg) or by "+" (approximately ≥ 5 - 10 kg)

Column 13. "Hoarseness". The sign "+" indicates obvious hoarseness. Normal voice at general talk is indicated by "0".

Column 14. "Vitreous opacities". Examination by ophthalmologist: "+" = typical opacities of the vitreous body without any other explanation than amyloid infiltration. "0" = no opacities at the time of the examination.

Column 15. "Blood pressure". The value of blood pressure in mm Hg at recumbent and upright position, respectively.

Column 16. "Tissue specimens confirming amyloidosis". The following abbreviations of biopsy specimens are used: N = sural nerve; S = skin; R = rectal mucosa; G = gastric mucosa; Gi = gingiva, M = skeletal muscle.
Column 17, "Comments". Some clinical manifestations of interest are given here. Figures refer to the patients age.

Columns 9 - 16. No sign is given in the table when examination was not performed or incompletely recorded or when information was uncertain.

Comments to Table II

Column 1. "Clinical numeral". See Table I.

Column 2. "Interval onset - diagnosis" is given in years. Onset refer to data in Table I, column 4. Diagnosis refer to age at examination when biopsy revealed amyloidosis ante mortem. The sign "p.m." indicates that amyloidosis was proved post mortem. In 5 cases histopathological examination was not performed: "-".

Column 3. "Age at death" in years.

Column 4. "Interval onset - death" is given in years and refers to data in Table I, column 4 and Table II, column 3, respectively.

Column 5. "Immediate cause of death". Information obtained from hospital records. It refers to clinical statement.

Column 6. "Age at inability to work". The figures indicate age in years when inability to work caused invalid pension. Information from the patients, their relatives or hospital records. No sign indicate capability of performing usual work. "?" = no or uncertain information.

Column 7 and 8. "Age at need of nursing" at home or at hospital. Figures indicate age in years when physical handicap necessitated nursing help in daily life, e.g. of dressing, eating, personal hygiene, moving in bed, getting into a chair.

Column 9. "Comments". Some examples of previous diagnoses are given here as well as some examinations performed at hospital.

Column 3 - 5. No sign indicates that the patient was alive in summer 1974.
Table I. Survey of clinical data of 60 patients with amyloidosis and polyneuropathy.

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<th>CLINICAL NUMERAL</th>
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<th>Sex</th>
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<th>Initial symptoms</th>
<th>Age</th>
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<th>Fasculations</th>
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<th>Weight loss</th>
<th>Housemans</th>
<th>Visceral specificity</th>
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<th>Renal</th>
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**Comments:**
- Duodenal ulcer, 42
- Duodenal ulcer, 38
- Chronic ulcers left foot
- Papilloma of urinary bladder
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</table>

- Pancreatic insufficiency, Malabsorption with polyneuropathy
- Chronic enteritis
- Amyotrophic lateral sclerosis
- Alcoholic polyneuropathy
- Myelography
- Arterial insufficiency of the legs. Arteriography. Myelography
- Amyotrophic lateral sclerosis
- Arterial insufficiency of the legs. Arteriography
- Myelography, Exploration of lumbar spinal cord. Addison's disease?
- The cutanea tarda type of porphyria
- Irritable colon
Table III. Age when the diagnosis of amyloidosis was histopathologically confirmed ante mortem in 49 patients with amyloidosis and polyneuropathy.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Range</th>
<th>Median</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>49</td>
<td>34 - 83</td>
<td>61</td>
<td>$59.8 \pm 1.84$</td>
<td>$12.9 \pm 1.29$</td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>34 - 83</td>
<td>63.5</td>
<td>$61.8 \pm 2.36$</td>
<td>$13.6 \pm 1.67$</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>35 - 75</td>
<td>59.5</td>
<td>$55.5 \pm 2.95$</td>
<td>$11.8 \pm 2.08$</td>
</tr>
<tr>
<td>Familial cases</td>
<td>33</td>
<td>34 - 83</td>
<td>61</td>
<td>$60.1 \pm 2.29$</td>
<td>$13.2 \pm 1.62$</td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>34 - 83</td>
<td>66</td>
<td>$63.9 \pm 2.83$</td>
<td>$13.3 \pm 2.00$</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>35 - 63</td>
<td>55</td>
<td>$52.5 \pm 2.95$</td>
<td>$9.8 \pm 2.08$</td>
</tr>
<tr>
<td>Proband</td>
<td>21</td>
<td>34 - 83</td>
<td>66</td>
<td>$63.9 \pm 2.88$</td>
<td>$13.2 \pm 2.03$</td>
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<tr>
<td>Secondary cases</td>
<td>12</td>
<td>35 - 68</td>
<td>56</td>
<td>$53.5 \pm 3.12$</td>
<td>$10.8 \pm 2.20$</td>
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<tr>
<td>Sporadic cases</td>
<td>16</td>
<td>38 - 75</td>
<td>58.5</td>
<td>$59.1 \pm 3.17$</td>
<td>$12.7 \pm 2.24$</td>
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<tr>
<td>Male</td>
<td>11</td>
<td>38 - 75</td>
<td>57</td>
<td>$57.7 \pm 3.73$</td>
<td>$12.4 \pm 2.64$</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>39 - 75</td>
<td>64</td>
<td>$62.0 \pm 6.33$</td>
<td>$14.2 \pm 4.49$</td>
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Table IV. Age at onset of symptoms in patients with amyloidosis and polyneuropathy.

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<th>Mean</th>
<th>S.D.</th>
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<td>I. All patients</td>
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<tr>
<td>Total</td>
<td>60</td>
<td>29 - 75</td>
<td>53.5</td>
<td>53.0 ± 1.47</td>
<td>11.4 ± 1.04</td>
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<tr>
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<td>40</td>
<td>29 - 75</td>
<td>55.5</td>
<td>54.4 ± 1.88</td>
<td>11.9 ± 1.33</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>33 - 70</td>
<td>51.5</td>
<td>50.1 ± 2.17</td>
<td>9.7 ± 1.53</td>
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<td>Familial cases</td>
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<td>29 - 75</td>
<td>54</td>
<td>52.6 ± 1.80</td>
<td>11.7 ± 1.27</td>
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<tr>
<td>Male</td>
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<td>29 - 75</td>
<td>56</td>
<td>55.0 ± 2.46</td>
<td>12.8 ± 1.75</td>
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<td>Female</td>
<td>15</td>
<td>33 - 63</td>
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<td>48.3 ± 2.14</td>
<td>8.3 ± 1.50</td>
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<tr>
<td>Non-familial cases</td>
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<td>35 - 72</td>
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<td>53.9 ± 2.59</td>
<td>11.0 ± 1.83</td>
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<td>II. Patients diagnosed</td>
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<td>Total</td>
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<td>29 - 75</td>
<td>55</td>
<td>53.7 ± 1.05</td>
<td>7.4 ± 0.74</td>
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<td>29 - 75</td>
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<td>55.9 ± 2.14</td>
<td>12.2 ± 1.50</td>
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<tr>
<td>Female</td>
<td>16</td>
<td>33 - 67</td>
<td>51.5</td>
<td>49.1 ± 2.52</td>
<td>10.1 ± 1.78</td>
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<tr>
<td>Familial cases</td>
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<td>29 - 75</td>
<td>54</td>
<td>53.4 ± 2.14</td>
<td>12.3 ± 1.51</td>
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<tr>
<td>Male</td>
<td>22</td>
<td>29 - 75</td>
<td>56</td>
<td>56.9 ± 2.75</td>
<td>12.9 ± 1.93</td>
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<tr>
<td>Female</td>
<td>11</td>
<td>33 - 56</td>
<td>47</td>
<td>46.3 ± 2.34</td>
<td>7.8 ± 1.66</td>
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<tr>
<td>Probandsl</td>
<td>21</td>
<td>29 - 75</td>
<td>56</td>
<td>56.3 ± 2.83</td>
<td>13.0 ± 2.00</td>
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<tr>
<td>Secondary cases</td>
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<td>33 - 63</td>
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<td>48.3 ± 2.69</td>
<td>9.7 ± 1.97</td>
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<td>Non-familial cases</td>
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<td>35 - 72</td>
<td>55</td>
<td>54.5 ± 2.87</td>
<td>11.5 ± 2.03</td>
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<tr>
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<td>11</td>
<td>36 - 72</td>
<td>53</td>
<td>53.8 ± 3.57</td>
<td>11.2 ± 2.38</td>
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<tr>
<td>Female</td>
<td>5</td>
<td>35 - 70</td>
<td>55</td>
<td>56.0 ± 5.98</td>
<td>13.4 ± 4.24</td>
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<td>Patients with diarrhoea</td>
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<td>29 - 69</td>
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<td>49.2 ± 2.85</td>
<td>11.4 ± 2.01</td>
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<td>Patients without diarrhoea</td>
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<td>33 - 75</td>
<td>55</td>
<td>55.6 ± 1.37</td>
<td>7.9 ± 0.97</td>
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</table>

See Table I, column 11.
Table V. Age at death of 27 patients with amyloidosis and polyneuropathy.

<table>
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<th>No.</th>
<th>Range</th>
<th>Median</th>
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<tbody>
<tr>
<td>Total</td>
<td>27</td>
<td>48 - 85</td>
<td>66</td>
<td>65.6 ± 1.90</td>
<td>9.9 ± 1.34</td>
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<tr>
<td>Male</td>
<td>20</td>
<td>48 - 85</td>
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<td>66.4 ± 2.41</td>
<td>10.8 ± 1.70</td>
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<tr>
<td>Female</td>
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<td>53 - 71</td>
<td>66</td>
<td>63.3 ± 2.45</td>
<td>6.5 ± 1.74</td>
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<td>Patients with diarrhea</td>
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<td>48 - 71</td>
<td>61</td>
<td>61.1 ± 2.13</td>
<td>7.4 ± 1.51</td>
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<tr>
<td>Patients without diarrhea</td>
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<td>54 - 85</td>
<td>68</td>
<td>69.2 ± 2.66</td>
<td>10.3 ± 1.87</td>
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</tbody>
</table>

*aSee Table I, column 11.

Table VI. Duration from onset of symptoms to death in 27 patients with amyloidosis and polyneuropathy.

<table>
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<tbody>
<tr>
<td>Total</td>
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<td>4 - 31</td>
<td>9</td>
<td>10.7 ± 1.17</td>
<td>6.1 ± 0.82</td>
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<tr>
<td>Male</td>
<td>20</td>
<td>4 - 31</td>
<td>9</td>
<td>11.3 ± 1.54</td>
<td>6.9 ± 1.09</td>
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<tr>
<td>Female</td>
<td>7</td>
<td>5 - 12</td>
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<td>8.7 ± 1.01</td>
<td>2.7 ± 0.72</td>
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<tr>
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<td>7.5</td>
<td>7.3 ± 0.57</td>
<td>2.0 ± 0.40</td>
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<td>5 - 31</td>
<td>12</td>
<td>13.4 ± 1.80</td>
<td>7.0 ± 1.27</td>
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</table>

*aSee Table I, column 11.
Table VII. Subjects belonging to family 1 and 2 in whom polyneuropathy was obvious but in whom no amyloid deposits were found at histopathological examination.

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<th>Genetical numeral</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical grading of neuropathy</th>
<th>EMG confirming neuropathy</th>
<th>No amyloid detected in tissues examined</th>
<th>Biopsy</th>
<th>Autopsy</th>
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<tr>
<td>1:IX:26</td>
<td>M</td>
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<td>Yes</td>
<td>Nerve x2&lt;sup&gt;b&lt;/sup&gt;, skin, rectum x2, muscle</td>
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<td>Heart, lung, liver, muscle, kidney, spinal cord</td>
</tr>
<tr>
<td>1:IX:27</td>
<td>M</td>
<td>57</td>
<td>+ +</td>
<td>Yes</td>
<td>Nerve x2, skin x2, rectum muscle x2, liver, esophagus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:IX:32</td>
<td>M</td>
<td>66</td>
<td>++ + + + +</td>
<td>Yes</td>
<td>Nerve, skin, rectum x2, muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:X:4</td>
<td>M</td>
<td>27</td>
<td>+ +</td>
<td>Yes</td>
<td>Nerve, skin, rectum x2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:X:5</td>
<td>M</td>
<td>54</td>
<td>++ + + + +</td>
<td>Yes</td>
<td>Skin, rectum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:X:9</td>
<td>F</td>
<td>31</td>
<td>+ +</td>
<td>Yes</td>
<td>Skin, muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:IV:38</td>
<td>M</td>
<td>70</td>
<td>+ +</td>
<td>Not examined</td>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:IV:47</td>
<td>M</td>
<td>78</td>
<td>+ +</td>
<td>Not examined</td>
<td>Skin, rectum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> + = slight; ++ = moderate; +++ = marked neuropathy.

<sup>b</sup> x2 = biopsy and examination at two different occasions.
Table VIII, Results of histopathological examination of biopsy specimens concerning amyloid deposits correlated to clinical grading of polyneuropathy.

<table>
<thead>
<tr>
<th>Results of histopathological examination&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Number of patients</th>
<th>Clinical grading of the polyneuropathy in the lower limbs&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloidosis confirmed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>Family 1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Family 2</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>No amyloid detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family 1</td>
<td>6</td>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Family 2</td>
<td>16</td>
<td>14&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Examination in polarized light after staining with alkaline Congo red.

<sup>b</sup>+ = slight; ++ = moderate; +++ = marked polyneuropathy. <sup>c</sup>Details are given in Table VII. <sup>d</sup>In most of these cases the signs and/or symptoms of polyneuropathy were slight. Only skin biopsy was performed.
Table IX. Sibships with at least one affected member.

<table>
<thead>
<tr>
<th>Affected</th>
<th>Normal sibs</th>
<th>Total sibs</th>
<th>Number of sibships</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>28</td>
<td>76</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>236</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41</td>
</tr>
</tbody>
</table>

Table X. Survey of sibships according to number of affected individuals and size of sibships.

<table>
<thead>
<tr>
<th>s = 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>r =</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>1</td>
<td></td>
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<td>1</td>
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</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>6</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

\[ S_r n_{sr} = 1 \quad 3 \quad 7 \quad 5 \quad 4 \quad 4 \quad 4 \quad 6 \quad 4 \quad 1 \quad 2 \quad 41 \]
\[ r_{min} = 1 \quad S_r n_{sr} = 1 \quad 3 \quad 9 \quad 12 \quad 6 \quad 7 \quad 8 \quad 10 \quad 14 \quad 2 \quad 4 \quad 76 \]
\[ S_r n_{sr} = 1 \quad 6 \quad 21 \quad 20 \quad 20 \quad 24 \quad 28 \quad 48 \quad 36 \quad 10 \quad 22 \quad 236 \]

s = size of sibships. r = number of affected sibs. \( n_{sr} \) = sibships of size s comprising r affected sibs in sibships involving at least one (\( r_{min} = 1 \)) affected sibs.
LEGENDS  Pedigrees 1-15

☐ Male  ☐ Both sexes
☐ Female  ☐ Four children
☒ Died

☒ Died before 25 years of age
<25

■ Polyneuropathy diagnosed at examination

☑ Signs and symptoms indicative of incipient polyneuropathy

☒ Reliably reported by relatives as polyneuropathy

† Amyloidosis proved histopathologically

† Biopsy negative for amyloidosis

• Examination performed by the author

‖ Consanguinity

✓ Proband

□ Numeral below symbol denotes number of
  the individual in the generation
Fig 2. Pedigree 2
Fig 3. Pedigree 3

Fig 4. Pedigree 4

Fig 5. Pedigree 5
Fig 6. Pedigree 6

Fig 7. Pedigree 7

Fig 8. Pedigree 8

Fig 9. Pedigree 9

Fig 10. Pedigree 10
Fig 11. Pedigree 11

Fig 12. Pedigree 12

Fig 13. Pedigree 13

Fig 14. Pedigree 14

Fig 15. Pedigree 15
Figure 16. Map of Northern Sweden with birthplaces of 60 patients with amyloidosis and polyneuropathy. Familial cases are designated by solid and sporadic cases by non-filled symbols. A map of the Nordic Countries is inserted with the relevant part of Northern Sweden indicated by lines.