Gastrointestinal Involvement in Familial Amyloidosis with Polyneuropathy

A clinical study

AKADEMISK AVHANDLING

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av

LARS STEEN

Umeå 1983
Familial Amyloidosis with Polyneuropathy was first recognized in Portugal and reported by Andrade in 1952. The disease is rare, but clustering of the patients has been reported from Portugal, Japan and northern Sweden. The gastrointestinal involvement in the Swedish form of the disease was studied in this investigation.

In a study of 52 patients on their first admission 47 displayed gastrointestinal symptoms in the form of severely altered bowel habits (intractable diarrhea and/or constipation). Steatorrhea was found in 30 out of 52 patients (58%) and an impaired d-xylose absorption in 26 out of 50 patients (52%). The steatorrhea was correlated to the degree of peripheral polyneuropathy as expressed by EMG-score. No relation could be established between steatorrhea or impaired d-xylose absorption with oral lactose and glucose tolerance tests indicating an intact enterocyte function.

A follow-up study comprising 21 patients demonstrated that all patients ultimately developed gastrointestinal symptoms and that the prevalence of diarrhea became higher with the duration of the disease. In this study steatorrhea became more frequent and was significantly related to the duration.

Bile acid breath test, fecal fat determination and d-xylose tests were performed on 13 patients. Six patients with results indicating an increased bile acid deconjugation in the small bowel were treated with antibiotics for one week, after which the results had returned to normal in all. Four out of five patients with impaired d-xylose absorption before treatment also returned to normal after antibiotics. Three patients with diarrhea 3-7 times daily were considerably relieved after treatment both concerning general well-being and bowel movements. The results give strong evidence that bacterial overgrowth of the small intestine is important in causing gastrointestinal dysfunction in this disease.

A histopathological study of the small intestinal mucosa on 27 patients showed that 84 percent were amyloid positive. The degree of amyloid infiltration did not correlate to the symptomatic state, steatorrhea or impaired d-xylose absorption. The surface ultrastructure was normal in all of 21 investigated cases.

Radiographical and endoscopical studies were performed on 43 patients altogether. Evidence of gastric stasis was found in 7 out of 37 patients investigated by means of gastric x-ray and in 7 out of 28 patients at gastroscopy. No characteristic radiological appearance of the disease could be shown in the small intestine, the colon or the gall bladder.

Nine patients who were operated on with the construction of an enterostomy were reported. The diversion of the fecal stream when the patients had diarrhea and were incontinent meant a considerable relief.

Key words: amyloidosis, electromyogram, malabsorption syndrome, gastric acid, gastroscopy, radioisotopes, radiography, intestinal mucosa.
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ABSTRACT

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To my Family
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ABBREVIATIONS

FAP = familial amyloidosis with polyneuropathy
EMG = electromyogram
SEM = scanning electron microscopy
DM = dissecting microscopy
LM = light microscopy
MAO = maximal acid output
OGTT = oral glucose tolerance test
DMSO = dimethyl sulfoxide
r = product moment correlation coefficient
r_s = Spearmans rank correlation coefficient
X^2 = chi square
BABT = bile acid breath test
The present thesis is based on the following papers:


V. Steen L, Ek B. Bile acid deconjugation and intestinal malabsorption in Familial Amyloidosis with Polyneuropathy; a consequence of the autonomic neuropathy of the gastrointestinal tract. In manuscript.

INTRODUCTION

Amyloidosis is characterized by the deposition of an homogenous, eosinophilic material in various tissues throughout the body. These deposits are responsible for the replacement and subsequent destruction of vital organs (14, 37). The clinical presentation depends upon the order and degree to which different organs or tissues are afflicted.

One constant feature of amyloid deposits is the presence of fibrils with a characteristic appearance (21). These fibrils have been shown by means of x-ray crystallography to be composed of a protein consisting of polypeptide chains arranged in an antiparallel conformation and beta-pleated sheet structure (28). The fibrils are the component responsible for the congo red staining and the green birefringence in polarized light (77, 88). Amyloid deposits and the subsequent disease processes are the first known pathologic process dependant on a unique protein conformation, that is not normally found in mammalian tissues (39).

Classification of amyloid
The original classification of amyloidosis by Reimann et al (90) into primary, secondary, tumorforming and associated with myeloma has been fairly durable. Classifications based on organ distribution and histological localization have not been generally accepted (55, 78). With the added knowledge of new syndromes, mainly heredofamilial amyloidosis and localized, organlimited forms the following new classification has been proposed (64):

1) Primary amyloidosis without evidence of preceeding or coexisting disease,
2) Amyloidosis with multiple myeloma;
3) Secondary amyloidosis (reactive systemic amyloidosis);
4) Localized amyloid; - single organ involvement without evidence of generalized amyloidosis;
5) Heredofamilial amyloidosis.
The development of advanced and highly sensitive analytical methods in recent years has permitted the isolation and characterization of amyloid fibrils. The amyloid's precursor polypeptides and their amino acid sequences in most of these entities are quite different and so probably are the mechanisms for formation and deposition in tissues of the various amyloid fibrils (39).

Several amyloid fibril proteins have been detected. In reactive systemic amyloidosis (formerly secondary amyloidosis) and the amyloidosis of Familial Mediterranean Fever, the presence of a protein designated AA has been demonstrated (67). The amyloid protein of primary amyloidosis, myeloma associated amyloidosis or immunocyte dyscrasias with amyloidosis, has been shown to consist of immunoglobulin light chains and is designated AL (36). Other amyloid proteins have been characterized in medullary thyroid carcinoma (104), in senile cardiac amyloidosis (109) and in familial amyloidosis with polyneuropathy type I where the protein is related to prealbumin (23, 103, 106).

Familial amyloidosis

Many descriptions of different amyloid syndromes with a genetic background have appeared in the literature (38, 107). Most of these are non-neuropathic or localized forms. The neuropathic heredofamilial amyloidoses are subdivided into four different syndromes according to their clinical presentation (38).

Familial Amyloidosis with Polyneuropathy (FAP) type I includes the cases reported from Portugal (5), Japan (6), Sweden (3, 4), Germany (26), Britain (112), USA (27), Brazil (58), Italy (11) and Spain (89). This type is dominated by a sensorimotor polyneuropathy affecting the lower extremities earlier and more severely than the upper. The polyneuropathy usually starts distally in the feet and moves eventually in a central direction causing an ultimate disability. Symptoms of autonomic polyneuropathy including sexual impotency, dyshidrosis, urinary retention and orthostatic hypotension are often troublesome features (4). Cardiac and pulmonary involvement have also recently been described (84). Gastrointestinal dysfunction have also been reported as well
as occasionally vitreous opacities (4, 5, 6, 61, 79, 91, 92). Type II is also called Rukavina or Indiana type and is characterized by the carpal tunnel syndrome and an early polyneuropathy of the upper extremities (96). Autonomic neuropathy has not been reported, but gastrointestinal symptoms may occur infrequently (38). Vitreous opacities are occasionally found (56, 71). Type III is dominated clinically by an early sensorimotor polyneuropathy of the lower extremities, which is followed by a later and less severe polyneuropathy of the upper ones. Autonomic symptoms develop in many patients. Duodenal ulcers were documented in six out of eight patients. Diarrhea and constipation occurred in a few patients, but was not as common as in type I. Nephropathy was both common and severe (1). This syndrome was described in Iowa in a family of Scottish, English and Irish descent and is sometimes called Iowa or van Allen type.

Type IV has been reported from Finland and Denmark (13, 75). This amyloid disease is characterized by a peculiar eye affliction known as corneal lattice dystrophy, cranial neuropathy and pendulous skin. Peripheral neuropathy of the extremities and gastrointestinal symptoms are an inconstant feature of this syndrome.

Gastrointestinal amyloidosis

Gastrointestinal involvement with a wide array of symptoms and dysfunction may occur in amyloidosis of different pathogenesis. In reactive systemic amyloidosis the underlying chronic illness usually dominates the clinical picture but often there are other organs involved including heart and kidneys as well as peripheral and autonomic nerves that will lead the clinician to suspect amyloidosis. Sometimes it is difficult to distinguish which symptoms are induced by the underlying disease and which by the amyloid infiltration (98).

Disturbances of gastrointestinal motility are encountered in all types of generalized amyloidosis and the cause has been ascribed to several pathophysiological mechanisms. Amyloid infiltration between gut muscle fibres may be a mechanical obstacle to contractility (34). Neuropathy of the gut nervous system is probably also important in causing disturbances of motility. The intrinsic nervous system of the colon was
infiltrated by amyloid in one patient where the sigmoid colon was surgically removed (15). Infiltration with amyloid has also been reported to occur in the sympathetic ganglia of the thoracodorsal chain (17) and in the cells of the intramural ganglia (82). Moreover, degenerative changes of the axones and replacement of intramural plexa by amyloid have been reported (98).

The clinical manifestations of changes in gastrointestinal motility include dysphagia and abnormal motility patterns at oesophageal manometry (34). In extreme cases the oesophagus become a tube-like aperistaltic organ simulating scleroderma (86). A delay in gastric emptying and in a few cases a severe gastric stasis has been reported (34, 54, 65).

A slowing down of the transit of barium has been shown to occur in the small intestine and at jejunal endoscopy the gut was aperistaltic (63, 111). Constipation and diarrhea singly or in combination are the most common symptoms (34, 98). One serious complication of decreased motility is intestinal pseudoobstruction i.e. clinical signs of mechanical ileus without obstructive changes of the lumen (66).

The small vessels of the intestinal wall are always engaged in amyloidosis involving the gastrointestinal tract (35). When larger mesenterial vessels are engaged possibly fatal complications may occur such as mesenterial occlusions, sometimes in combination with hypotension, which have been reported as causing ischemic damage (47, 73). Thus ischemic colitis due to amyloid infiltration of the mesenteric vessels has been described (16, 24).

Bleeding from the gastrointestinal tract is believed to be a result of increased fragility of small vessels or by microinfarctions (34) since no coagulation disturbances have been found in patients with amyloidosis (57). The clinical expression ranges from small petechial lesions to severe blood loss (62, 68, 83). In five patients who had documented episodes of gastrointestinal bleeding it was not possible to find the source of the bleeding either during life or at an autopsy (57). Gastric and duodenal ulcers as well as small jejunal erosions (111)
have been reported in several cases and may also be a source of gastro-intestinal blood loss (16, 40, 70, 76). It has been suggested that the ulcers were caused by vascular insufficiency due to amyloid deposits in the vessels (16). In addition, hemorrhagic erosions of the gastric mucosa have been described (98).

Spontaneous perforations of the intestinal wall without previous known ulceration have been reported to occur in the oesophagus, the small intestine and the rectum. These are believed to be caused by massive infiltration of the bowel wall (2, 34, 44, 46).

A few cases with rectal bleeding associated with changes that very much resembled ulcerative colitis have been reported in the literature (19, 20). The amyloidosis in such cases may be secondary to a chronic ulcerative colitis (102).

Localized tumorlike amyloid masses, either small, single or multiple polypoid lesions or large cancerlike and lumenobstructing processes, are known to occur. They may cause stenosis in any segment of the gastrointestinal tract and bleeding is sometimes a clinical problem in these cases (10, 20, 24, 35, 53, 64, 99, 108).

The prevalence of malabsorption syndrome in non-characterized amyloidosis is reported to be rather low. In a series of 236 cases only 5 percent displayed well documented malabsorption (64) and in another series 6 patients out of 103 had signs of malabsorption (48).

The pathogenesis of intestinal malabsorption in amyloidosis has not yet been fully clarified. Different pathophysiological mechanisms may be operating in different types of amyloidosis as well as in individual patients. The enterocytes, however, seem to be unaffected in the great majority of cases, except in very severe cases in which massive deposits may induce local mucosal destruction (10, 34). Vascular insufficiency of the mucosa could be a likely cause in some cases (48). It has been proposed that subepithelial deposits act as a mechanical barrier for absorption (34, 98). A decreased peristalsis with subsequent in-
testinal stasis and a secondary bacterial colonization of the small intestine is also a possible explanation for malabsorption in some cases but no firm evidence for this has been put forward in patients with amyloidosis without polyneuropathy. An exocrine pancreatic insufficiency could be caused by massive amyloid deposition with subsequent acinar destruction of the pancreas (19).

**Gastrointestinal involvement in FAP - Type I**

Gastrointestinal dysfunction is very common in neuropathic amyloidosis of type I. In large series, virtually all the patients had either diarrhea or constipation or both alternating (6, 25, 61, 79, 91, 92). The reason for those symptoms may be amyloid infiltration of the bowel wall (80), but the most common explanation seems to be a disruption of the neurogenic control of the bowel motility (18, 32, 79). The presence of amyloid deposits has been demonstrated in the extrinsic and the intrinsic autonomous nervous system of the gut (18, 32, 49, 51, 79, 95). In biopsy specimens from the rectal mucosa the adrenergic intramural nerves have been shown to be depleted of catecholamines (95). Furthermore, the number of preganglionic autonomic cells was reduced in four patients with neuropathy and orthostatic hypotension (69).

The clinical manifestations of motility disturbances may be derived from any segment of the gastrointestinal tract. Oesophageal dysmotility in combination with dysphagia have been reported (9, 49, 97). Gastric retention with nausea and vomiting have been described, especially from Portugal (15, 49, 79, 91, 92). Gastric stasis has been believed to be the cause of a substantial part of the gastrointestinal dysfunction (79). Gastric secretion tests have revealed hypochlorhydria in six and achlorhydria in two out of nine investigated patients (91, 92). The Hollander test was frequently negative in spite of a good response to histamine stimulation (52, 79). Radiological investigations of the small intestine have only very seldom revealed anatomical changes and in those cases only in the form of deficiency patterns, thickened folds or megalobulb. On the other hand, slow transit of barium and hypomotility have been reported more often (15, 18, 48, 79, 92, 95), whereas rapid transit of barium has been found in one patient (32).
Bleeding or perforation of the gut have not been noted as a problem in FAP, except in one case where necrosis of a segment of the sigmoid colon necessitated an acute operation with the construction of a colostomy (15).

A review of the literature on the gastrointestinal symptoms and laboratory investigations in FAP is outlined in Table I. For 123 reported patients it was possible to obtain data on the frequency of gastrointestinal symptoms, mainly in the form of altered bowel habits occurring in 117 patients. Probably all 483 Portuguese patients had gastrointestinal symptoms (25). Kito also reported a large series of Japanese patients with constipation and diarrhea that probably afflicted all of them (61). The prevalence of gastrointestinal symptoms may be somewhat lower in the "late onset" type of FAP as reported from Portugal (8).

Steatorrhea was found in 14 out of 30 investigated patients (Table I). Monteiro, however, reported that fecal fat output was "almost always normal" in his material of 35 patients (79). The Triolein test (87) was positive in 43.5 per cent in one study and in 3 out of 7 patients in another (79, 92). In Japanese patients with FAP fecal fat output was normal in 10 investigated patients (6). Neither Monteiro, nor Araki, however, give any details as to the methodology used for measuring fecal fat output. The d-xylose absorption was impaired in 18 out of 25 investigated patients (Table I). In addition, decreased d-xylose absorption was found in 37.5 per cent of the patients in a Portuguese study and was explained by a defective gastric emptying in most cases (79). The Schilling test was found to be abnormal in 4 out of 10 investigated patients (18, 48, 80, 89, 93, 95). Reports have appeared with descriptions of small bowel biopsies performed in 27 patients (see Table I). The villous structure was normal in all cases except one who had "a minimal coeliac disease" that did not respond to a gluten-free diet (72).

The pathophysiological mechanism causing intestinal malabsorption of fat and d-xylose is obscure and may be multifactorial (98). Amyloid deposits in the subepithelial space, the muscularis mucosa and the sub-
mucosa could create a mechanical barrier inhibiting the absorption (34) or induce a vascular insufficiency of the tissue (48). Theoretically, steatorrhea may be caused by an exocrine pancreatic insufficiency as amyloid substance has been demonstrated in the pancreas in FAP (51). However, stimulation tests of the pancreas have been reported to be normal (32, 79, 93).

Table I. Review of the literature on FAP type I where fat malabsorption, d-xylose absorption, the villous structure and gastrointestinal symptoms have been investigated. Number of patients with abnormal findings (a) and number of performed tests (b) are expressed as a/b.

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<th>Author(s)</th>
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123 14/30 18/25 0/27 117

TT 4/8
Dysmotility, secondary to an autonomic neuropathy, of the small intestine with a subsequent bacterial overgrowth has been suggested as a cause of the malabsorption (49), and has also been proved to exist in two cases with steatorrhea by means of the $^{14}$C-cholyl-glycine breath test (30).

**Aims of the study**

Motility disturbances with diarrhea, constipation or both of them alternating have been described in the Swedish form of FAP type I. Intestinal malabsorption as indicated by steatorrhea was found in 7 out of 12 investigated patients with FAP at the unit for gastroenterology at this hospital and reported by Andersson (4). These 12 patients are included in Study I. The clinical problems induced by the gastrointestinal involvement are frequent and sometimes dominate the symptomatology of the patients with FAP. The great clinical importance of the gastrointestinal manifestations of FAP triggered the interest in the disease and gave rise to this investigation. The main aims of the study were:

- to study the gastrointestinal symptoms and their evolution during the course of FAP and to relate them to the peripheral polyneuropathy of the disease
- to investigate the prevalence of intestinal malabsorption and some possible pathophysiological mechanisms
- to study the morphology of the jejunal mucosa in relation to symptoms and presence of intestinal malabsorption
- to study the radiological and endoscopical appearance of the gastrointestinal tract
- to describe the results of enterostomy operations on 9 patients.

**MATERIAL**

The patient material consisted of patients with familial amyloidosis with polyneuropathy (FAP) type I. The criteria for the diagnosis were 1) histological verification of amyloid deposits in biopsies from rectal mucosa and/or skin stained by alkaline congo red and examined in polarized light giving a typical green birefringence (33) and 2) peri-
pheral polyneuropathy with a typical clinical pattern, in most cases also verified by electromyogram. The patients were thoroughly investigated in order to exclude other types of amyloidosis such as chronic illnesses with secondary amyloidosis and myeloma or related disorders. The patients were also examined with regard to other causes of polyneuropathy e.g. diabetes mellitus, pernicious anemia, alcoholism and other neurological diseases.

Fifty-two patients, 34 males and 18 females, were investigated consecutively at the unit for Gastroenterology, Department of Medicine, University Hospital of Umeå. Their gastrointestinal symptoms at the onset of FAP and on admission to the hospital were recorded. All the patients went through a gastrointestinal investigation and the study was based on their case records (Study I). In addition 42 patients were given tests for gastric acid secretion.

All patients were offered the possibility of a follow-up regardless of the stage or severity of the disease. In some cases this was refused because of advanced age and in other cases because of the long journey to this hospital. When the follow-up period had reached the duration of three years the patient was included in this study which then comprised 21 patients who had been in the follow-up for between 3 - 10 years. The patients were all seen several times at the hospital during the follow-up period and were not selected in any way (Study II).

Twenty-seven patients with a verified diagnosis of FAP were subjected to a small bowel biopsy. The specimens were examined by means of dissecting microscopy, light microscopy and scanning electron microscopy (Study III).

Radiographic examinations of the gastrointestinal tract and the gall bladder were performed on 43 patients altogether and of these, 28 had also been investigated by means of an upper gastrointestinal endoscopy (Study IV).

Thirteen patients with known FAP were investigated by means of the bile acid breath test (BABT), fecal fat determination and d-xylose test.
Those with abnormal BABT were treated with antibiotics for one week and the tests were reported (Study V).

Three patients with an advanced stage of FAP had undergone the construction of an enterostomy (Study VI). Since the report was written six new patients have appeared and have been operated on for the same reason and using the same technique. They are now included in the thesis.

METHODS

Clinical assessment
The peripheral neuropathy was graded clinically as follows:
Grade 1: Subjective symptoms of polyneuropathy.
Grade 2: Subjective symptoms of polyneuropathy and minor motor dysfunction.
Grade 3: Subjective symptoms of polyneuropathy and major motor dysfunction necessitating functional support.
Grade 4: Total disability with the patient in a wheelchair or bedridden.

In grades 1 and 2 the patients were able to undertake most of the normal activities of daily life as usual and to keep on working. Grades 3 and 4 meant a reduced ability to cope with everyday activities and most patients had to retire from their work.

EMG
Electromyograms were made according to a standard technique using concentric needle electrodes. Because the neuropathy in FAP type I is of an axonal type indicating that the primary site of the lesion is in ventral horn cells, ventral roots and spinal ganglia (12), conduction velocities are poor indicators of the neurological damage FAP causes. Therefore the extent of the neurological damage was evaluated by estimating the loss of motor unit activity in the anterior tibial muscle bilaterally. The EMG results were classified according to the following scoring:
Score 0: Normal interference pattern
Score 1: Slight loss of motor units estimated as less than 25 percent
Score 2: Moderate loss of motor units estimated to be within the range 25 - 75 percent
Score 3: Pronounced but not total denervation, estimated as more than 75 percent
Score 4: Total loss of motor unit activity.

Biopsies
Biopsies for histological verification of the amyloidosis were obtained from the rectal mucosa, the skin, the small intestine and the stomach. The biopsy specimens were stained by alkaline congo red and examined in polarized light (33).

A biopsy of the small intestine was obtained by using a Watson biopsy capsule which was advanced to the ligament of Treitz with the help of an upper gastrointestinal fibreoptic endoscope (Olympus GIF-Q). The aspiration tube was located in the biopsy channel of the endoscope. With the tip of the endoscope in the descending part of the duodenum the capsule was guided down a further 20 - 30 cm and then suction was applied. The biopsy specimen was gently removed from the capsule and divided into two halves. The half that was destined for Scanning Electron Microscopy (SEM) was immediately fixed in phosphate buffered (6.25%, pH 7.2 - 7.4) glutar aldehyde, while the other half, destined for Dissecting Microscopy (DM) and Light Microscopy (LM) was mounted on millipore filter and the villous structure was examined in the Dissecting Microscope (Nikon) and thereafter fixed in neutral formalin.

Microscopical techniques
The specimens assigned for LM examinations were embedded in paraffin, orientated and cut serially parallel to villi and crypts and stained with hematoxylin-eosin as well as with alkaline congo red. The sections stained with congo red were examined both with directly transmitted illumination and with polarized light (33). The structure of the mucosa was assessed according to Whitehead (110).
The first stage in the preparation for Scanning Electron Microscopy (SEM) was the flushing of the mucosal surface with 5 ml isotonic NaCl. The specimens were then dehydrated in rising concentrations of ethanol, thereafter transferred into iso-amylacetate in rising concentrations and dried from liquid carbon dioxide in a critical-point-drying apparatus (Polaron E 3000). The specimens were coated with approximately 20 nm gold in a modified vacuum unit during automatic tilting and rotation (Edwards Vacuum Coating Unit, Mod. E12-E14). They were then examined in a Cambridge S-4 Scanning Electron Microscope, operated at 10 and 20 KV accelerating voltage and with a final aperture size of 40 nm. Each specimen was studied at three different magnifications during the same sequence: 1) at low magnification (x100), the general architecture of the small intestinal mucosa was assessed; 2) at medium magnification (x1000), its villous structure was studied and 3) at high magnification (x10 000), its surface ultrastructure was analysed.

Endoscopy and radiology
An upper gastrointestinal endoscopy was performed after an overnight fast. A few patients received 5 mg diazepam intravenously about 15 minutes before the investigation. After application of a local anaesthetic the endoscope (Olympus GIF-Q or GIF-K) was inserted. All abnormalities were noted and special attention was paid to the peristalsis of the antrum and canalis part of the stomach as well as to the pyloric function.

The radiological investigations were carried out using the normal techniques of the laboratory. After an overnight fast the contrast media (barium sulfate and water) were administered orally. The stomach was examined by fluoroscopy and several exposures were made. The small intestine was then examined by single exposures until the barium front had reached the terminal ileum and colon. The time at which the front reached the caecum was recorded as the barium transit time. In 15 control subjects the mean transit time was 210 minutes, the standard deviation was 113 minutes (range 30 - 420) (31). The terminal ileum was examined fluoroscopically. After a thorough evacuation the patients were given a barium enema. Several exposures were made followed by a
post evacuation film. Cholecystogram was carried out by giving the patients 3 grams of Biloptin\textsuperscript{R} the night before the investigation, which was itself preceded by an overnight fast. The gall bladder was visualized by fluoroscopy and the patients without gall stones received 50 ml Emtobil\textsuperscript{R} (Astra-Meditec) to stimulate the emptying of the gall bladder.

**Acid secretion tests**
Pentagastrin tests for maximal acid output (MAO) were carried out. The patients received 6\textmu g pentagastrin per kg body weight subcutaneously and the gastric secretion was collected at 15 minute intervals. Prior to the test the site of the collection tube was checked with the infusion and recovery of water. MAO was calculated as the mean of the four periods with the highest secretion and expressed as mmol/hour HCl. Hypoglycemia was induced by giving insulin intravenously with simultaneous monitoring of blood glucose (Hollander test). The gastric secretion was collected and measured as described above. In all cases an adequate decrease in blood glucose was achieved (less than 2.0 mmol/l) (52).

**Malabsorption tests**
Fecal fat determinations were carried out during the stay in hospital. Before the examination the patients had 40 extra grams of fat per day in addition to their usual diet at home. The collection period lasted 72 hours in most cases. When they were constipated the collection period was extended by 24 or 48 hours. During the collection period the patients were given a standard hospital diet plus 40 grams extra fat. The amount of ingested fat was calculated as at least 100 grams daily. The amount of fecal fat was calculated according to van de Kamer (59) and expressed as grams per 24 hours. Sixty-five healthy controls had a mean value of log 0.4915 grams/24 hours with a standard deviation of log 0.1907 corresponding to 3.1 grams/24 hours and 1.6 grams respectively. The upper normal limit of 6.0 grams/24 hours was calculated from the mean value plus 1.5 standard deviation (29).
After an overnight fast 25 grams of d-xylose in 500 ml water was administered orally. The urine was collected for 5 hours and the amount of d-xylose in the urine was estimated according to Roe and Rice (94). The urine was evaluated for volume and creatinine, and serum creatinine was measured. A five-hour creatinine clearance could then be calculated. If an incomplete urinary collection was suspected the test was repeated and if the renal function was impaired the test was excluded from the study.

Bile acid breath test (BABT)

Five μCi of glycine-1-¹⁴C-cholic acid (Radiochemical Centre, Amersham) was administered orally in 200 ml of juice after an overnight fast. The breath was collected at hourly intervals in a trapping solution containing 1 mmol hyamine hydroxide according to Sherr et al. (101). The radioactivity was measured in a liquid scintillation counter (Beckman LS 2800). The cumulative specific activity of expired ¹⁴CO₂ breath was obtained by measurement of the area under the curve from zero time to six hours. The values were expressed as total ¹⁴CO₂ breath excretion/4 hours and 6 hours (percent of administered dose). The upper normal limit for this method was 1.5%/4 hours and 3%/6 hours. The reference values from the Department of Clinical Chemistry, Karolinska Sjukhuset, Stockholm were used. This reference value was checked on 10 healthy controls without history of gastrointestinal disease of gastrointestinal symptoms. The mean age was 36.7 years (range 28-50), 6 were females and 4 were males. The cumulated value was 0.47% at 4 hours (S.D. 0.33) and 1.36% at 6 hours (S.D. 0.94).

An oral lactose load was performed after an overnight fast after which the patients received 50 grams of lactose in 500 ml water perorally. Afterwards blood glucose was measured at 0', 15', 30', 60' and 90'. The difference between the zero level and peak level was calculated. A difference of more than 1.3 mmol/l was regarded as normal.

An oral glucose tolerance test (OGTT) was carried out after an overnight fast. The patients were given 50 grams of glucose in 500 ml
Blood glucose was measured at 0', 30', 60', 90', 120', 150', 180', 210' and 140'.

Blood chemical analyses were made using standard laboratory tests, including hemoglobin level, serum levels of iron, folate, B12 and magnesium as well as plasma levels of calcium, phosphate, potassium, sodium and albumin.

Statistical evaluation
The data were calculated statistically by means of the Wilcoxon Rank Sum Test, the Spearman Rank Correlation Test, Productmoment correlation and Chi square test (105).

RESULTS AND DISCUSSION

Gastrointestinal symptoms
The onset of FAP was a peripheral polyneuropathy in 39 out of 52 patients. One patient had postural hypotension as the initial symptom. The remaining 12 patients had gastrointestinal symptoms beginning simultaneously with the neurological symptoms in 8 cases and prior to them in 4 cases. On first admission 47 out of 52 patients presented gastrointestinal complaints, the most common being alterations in the bowel habits. Constipation either alone or relieved by bouts of diarrhea was present in 27 patients, while diarrhea either constant or in periods was encountered in 20 patients. From the onset until admission diarrhea became increasingly frequent. Nausea and vomiting was a problem of clinical importance in nine patients (I).

Twenty-one patients were followed up for three years or more from the time of diagnosis. All patients eventually developed gastrointestinal symptoms and there was a striking tendency towards an increasing prevalence of diarrhea. Thus, 15 out of 21 had diarrhea, 4 had alternating constipation and diarrhea, while 2 were constipated at the end-point of the study. The development of a more severe peripheral polyneuropathy, grade 3 and 4, was related in time and frequency to the appearance of
Fecal incontinence, urinary retention and postural hypotension. Fecal incontinence eventually occurred in 13 patients. All 6 patients who remained in the follow-up nine years after diagnosis were incontinent (II).

The main gastrointestinal symptoms in FAP are related to a motility disturbance that is probably caused by amyloid deposits in the intrinsic and extrinsic autonomous nervous system of the gut (18, 32, 49, 51, 79, 95). The prevalence of diarrhea and constipation is high in FAP and all the Swedish patients ultimately developed them (II). The findings agree with those reported from Portugal (79, 92) and Japan (6, 61) and with other reports as well (see Table I). The pattern of changed bowel habits also seems to be similar in the Swedish, Portuguese and Japanese varieties of FAP type I, especially the peculiar combination of alternating constipation and diarrhea.

Loss of body weight was encountered in all patients except one in this study (II). It correlated closely to the progress of the disease and in the Swedish patients was probably caused by a combination of malabsorption, nausea and vomiting with concurrent anorexia and muscular atrophy (4). On the other hand, the weight loss among the Portuguese patients was sometimes an early feature and is probably, therefore, not related to malnutrition (25).

Gastric studies

Pentagastrin stimulation tests were performed in 42 patients and the results are presented in Table II. Thirty-two patients were hypo- or achlorhydric (below 16.4 mmol/h in males and below 13.5 mmol/h in females). There was a weak correlation between steatorrhea and diminished MAO (r = 0.33 n.s.) An insulin stimulation test (Hollander test) was carried out on 17 patients and the results are plotted against pentagastrin test results in Figure 1. Ten patients had an insulin stimulated MAO that was less than 50 per cent of the corresponding pentagastrin test.
### Table II. Gastric acid secretion tests in 42 patients with FAP.

<table>
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<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Duration</th>
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<th>Hollander test (MAO)</th>
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The frequency of hypo- or achlorhydria in FAP is rather high in both the Swedish and the Portuguese patients (79, 92). In studies on patients from Japan or the USA, however, they have been judged normal (6,
The influence of age on the gastric secretion of HCl has been a matter of debate, and could be one explanation for the high prevalence of hypochlorhydria as the mean age of the Swedish patients investigated is rather high. Older patients secrete less acid (45) but correction for height abolishes this relationship (50). The mechanism behind the hyposecretion of HCl could be that of "amyloid vagotomy". The Hollander test seems to support such an assumption as some patients with normal pentagastrin stimulated secretion had a low response on adequate insulin stimulation (79) (Table II, Fig. 1).

Radiographic examination of the stomach and duodenum were performed in 37 patients. Contrast defects that indicated solid residues were found in 7 patients without any anatomical change of the distal stomach, pylorus or duodenum which could explain it. Five patients were judged to have increased fluid in the stomach at the beginning of the investigation.
An upper gastrointestinal endoscopy was performed in 28 patients who had all been investigated by means of gastric x-ray. Seven patients had solid residues in spite of an overnight fast. Four of these patients did not have visible peristalsis of the antral-pyloric region during at least five minutes of observation. One of the patients with gastric retention had a prepyloric ulcer which may have caused the retention. A further five patients displayed an inactive antral-pyloric region, of whom two had large atonic stomachs. Three patients were found to have peptic ulcers. One of these had a prepyloric ulcer and a low value for the pentagastrin test (2.8 mmol/h). The other two patients, one with gastric and one with duodenal ulcers, had normal or high MAO (20.0 and 27.3 mmol/h respectively). One patient had a deformed canalis part of the stomach and a MAO value of 17.2 mmol/h (IV) (Table II, Fig. 1).

The radiological and endoscopical studies on the stomach in FAP have mostly shown evidence of gastric stasis that in the majority of the cases could not be explained by an anatomical stenosis. The periodicity of this gastric retention as reported in the Swedish (IV) as well as in the Portuguese patients (79) is not easily explained, but could possibly be a result of changes in the autonomic nervous tone in the pyloric region that were in some instances abolished by the forced passage of an endoscope through the pylorus (IV).

Peptic ulcers occurred in three patients and post-ulcerative deformation of the canalis part of the stomach in one. Three had normal or somewhat high HCl secretion. The combination of amyloid in the small vessels of the gut wall (51) with reduced blood flow and/or decreased protective properties and a somewhat high HCl secretion might have caused the peptic ulcers.

Intestine
Thirty-one patients were subjected to radiographic examinations of the small intestine. Two patients had a fast barium transit time of ½ hour while one had an delayed transit time of 8 hours. All the other patients had transit times within the range 1 - 6 hours. There were no correlations between barium transit times and steatorrhea or impaired
D-xylose absorption. Flocculation of the contrast medium was found in three cases of whom one had steatorrhea. Apart from one patient with coarse mucosal folds no gross anatomical changes were detected. Barium enemas were given to 36 patients and in one fecal impaction of the rectum with secondary stercoral diarrhea was found. Colonic diverticula were demonstrated in 7 patients. All the other examinations were judged as normal (IV).

Conventional radiological methods revealed that the great majority of the patients investigated displayed neither motility disturbances nor gross anatomical changes of the intestines. It should be noted, however, that barium is a heavy and unphysiological contrast and probably does not give a true picture of the motility under physiological conditions. In amyloidosis secondary to chronic illnesses or immunocyte dyscrasias with gastrointestinal involvement, anatomical changes with thickening of the valvulae coniventes are known to occur (100) as well as thickening and atonicity (86). Marked delay in barium transit has also been reported (65). These finding contrast to those reported in FAP where only a few cases are reported to have deficiency patterns (48). However, slow barium transit has been reported in FAP from Portugal (79, 92), but this phenomenon could not be confirmed in the Swedish patients with FAP (IV).

Small bowel biopsies were obtained in 27 patients (III). The dissecting microscopy was assessed as normal in all cases. The specimens from 25 patients were analyzed in the light microscope and an ordinary villous structure was found in all cases. Amyloid substance could not be detected in 4 cases, but in 2 of these the biopsy was taken too shallowly to allow assessment of the submucosa. Amyloid deposits were demonstrated in the submucosa exclusively in 10 patients, in the submucosa and the muscularis mucosae in another 8 patients and in the submucosa, the muscularis mucosae and the lamina propria in 3 patients. In no case could amyloid infiltration be detected in the enterocytes. The amount of amyloid was more abundant in the submucosa when it was also present in the muscularis mucosae and even more so when deposits were detected in the mucosa as well. There were no correlations between the degree of amy-
loid deposits and the finding of steatorrhea or diminished d-xylose absorption. Nor were there any statistically significant differences between the degree of amyloid deposits and the symptomatic state of the patients.

Scanning electron microscopy was carried out on the small bowel biopsy specimens of 21 patients (III). A normal mucosal architecture was confirmed in all cases. The ultrastructure was completely normal in 16 cases whereas the glycocalyx was decreased in five patients. In one of the latter rod-shaped microorganisms were detected adhering to the villous surface. These five patients did not, however, differ from the other patients regarding their symptomatic state or the malabsorption tests.

The histological and ultrastructural findings excluded the possibility of villous atrophy as a cause of the intestinal dysfunction. Similar results were found in the Portuguese patients with FAP (79). If the two patients with too shallow biopsies are excluded it is clear that small intestinal biopsies have a high frequency of positive amyloid reaction in the specimens. This could be used in gastrointestinal screening of obscure malabsorption syndromes where an obligatory small intestinal biopsy could easily be stained by alkaline congo red and examined in polarized light. The results indicate that the amyloid deposits in the mucosa, the muscularis mucosae and the submucosa are not the main cause of the gastrointestinal dysfunction of FAP.

The role of the glycocalyx deficiency in intestinal absorption is not understood. The adherent microorganisms on the villous surface in one patient may suggest that colonization of bacteria in the small intestine could cause gastrointestinal dysfunction in some instances.

Malabsorption
Three patients out of 44 had an abnormally small rise in blood glucose level (less than 1.3 mmol/l) after an oral lactose load. All of these patients had normal oral glucose tolerance tests (OGTT). OGTT was carried out on 41 patients of whom one had a diabetic OGTT curve and one had a flat OGTT curve. All the other patients had curves well within the normal limits (I).
Serum electrolytes were within the normal range in almost all patients. Serum albumin was below normal in 8 patients, who all, except one, had steatorrhea (I). Serum albumin was plotted in relation to the duration of symptoms and did not show any significant correlation. However, the majority of the low albumine values were encountered after the symptoms had lasted five years. The material was divided into observations made 0 - 5 years after the onset and five years or more after the onset and the proportions of patients with low and normal serum albumin were compared showing a statistically significant difference between the groups ($x^2 = 7.0; p < 0.01$) (II).

One patient had a low serum B12 and another had a value close to the lower normal limit out of 45 analyzed. Neither of those two patients presented anemia. Serum folate was reduced in 10 out of 45 patients investigated. Seven out of these 10 patients had an increased fecal fat output (I).

Anemia was encountered in 10 patients out of the 52. One of these had a microcytic and sideropenic anemia and the remaining nine patients had normocytic and normochromic anemia. Five of the anemic patients had low serum folate levels, but in no case could macrocytic or megaloblastic features, either in peripheral blood or bone marrow aspirates, be demonstrated (I).

Steatorrhea was found in 30 out of 52 patients investigated and an impaired d-xylose absorption in 26 out of 50 patients (I). The correlation coefficient between steatorrhea and the d-xylose test was 0.37 using the Spearman Rank Correlation test (105) ($p < 0.01$). The duration of FAP symptoms did not correlate to fecal fat output or impaired d-xylose absorption. The patient group with constant diarrhea had a high prevalence of steatorrhea and impaired d-xylose absorption. The higher the patient's emg-score the greater the chance of his having steatorrhea. Thus, the difference between score groups 0 - 1 and 3 - 4 was statistically significant as calculated by Wilcoxon's Rank Sum test ($p < 0.01$) (105) (I).
During the follow-up steatorrhea was shown in 19 out of 21 patients at some time, but there was a considerable variation from low normal to high fecal fat output in some patients. There was a significant tendency towards a higher fecal output of fat with a longer duration of symptoms (II).

The high prevalence of steatorrhea as described in studies I and II is not consistent with that reported from Portugal (79) and Japan (6). The Triolein test employed in two Portuguese reports, however, indicates that malabsorption of fat may be present (79, 92), but the Triolein test is not as sensitive or accurate as the determination of fecal fat (87). However, the review of probable FAP type I cases excluding the Portuguese and Japanese patients (see Table I) where determinations of fecal fat have been performed indicates a prevalence of steatorrhea that agrees with the findings in the Swedish cases (I, II). The lack of agreement between the Swedish patients and the Portuguese or Japanese ones may be explained by methodological differences. The prevalence of steatorrhea increased with more pronounced neurological damage as expressed by emg-score, and did also correlate significantly with the duration of the symptoms in the follow-up. Thus, it is probable that the severity of the neuropathy as well as the duration of the symptoms determine the development of steatorrhea.

The d-xylose absorption was impaired in about half the patients (I), a frequency that is consistent with that reported by Monteiro (79) and somewhat lower than that described by do Rosario (92) as well as with the frequency in the cases reviewed (Table I). Impaired kidney function was excluded (I), but in some cases gastric stasis may have caused a decreased d-xylose absorption (IV) (79).

The bile acid breath test was carried out on 13 patients. Six had increased deconjugation of labelled bile acids. Seven patients had normal values of the BABT but it should be noted that four of these patients recently had been treated with antibiotics for other reasons. There was a trend towards higher fecal fat output and lower d-xylose absorption in the patients with abnormal BABT, but this difference was not statis-
tically significant. The six patients with abnormal BABT were treated for one week with a combination of doxycycline and metronidazole. After the treatment period the BABT returned to normal values in all patients. In addition, out of 5 patients with an initial low d-xylose absorption, 4 regained normal values after antibiotics. Four out of five investigated patients had an increased fecal fat output in the group with abnormal BABT and after antibiotic treatment the three patients with the highest output of fecal fat reduced their output but none became normalized (V).

The pathogenesis of the steatorrhea and impaired d-xylose absorption in FAP is unclear and possibly multifactorial (98). The villous structure and the surface ultrastructure were unaffected (III). The high proportion of normal OGTT's and oral lactose tests also indicates an unaffected enterocyte function. There was no correlation between the amount of amyloid in the biopsy specimens from the small intestine and the presence of steatorrhea or impaired d-xylose tests. Thus, amyloid deposits in the mucosal layers do not seem to act as a mechanical barrier to absorption except possibly in advanced cases. The extrinsic and intrinsic autonomous nervous system of the gastrointestinal tract have been shown to be involved in FAP (18, 32, 49, 51, 69, 79, 95). Through a disturbed motility and achlorhydria this could induce a bacterial colonization of the small bowel lumen. Several strains of bacteria are known to deconjugate bile acids and to metabolize d-xylose (41, 42, 60). The results of the BABT clearly demonstrate that bile acid deconjugation occurs in FAP. In the absence of other possible causes for bile acid malabsorption the reason for this deconjugation is probably bacterial overgrowth of the small intestine. Antibiotic treatment normalized the BABT in all cases and improved the d-xylose absorption as well as the patients gastrointestinal symptoms. This is also indirectly indicative of bacterial contamination of the small bowel, which may be corrected with antibiotic treatment. The failure of the antibiotic treatment to influence the fecal fat output more than marginally is not easily explained, but it has been suggested that bacterial toxins may give structural changes of the small intestinal mucosa, which possibly could persist some time after treatment (60). The BABT was also reported to be indicative of
deconjugation of bile acids in two patients with steatorrhea (30). Other possible causative factors of malabsorption such as an exocrine pancreatic insufficiency and a deranged mucosal circulation have not been investigated.

Treatment

Nine patients were operated for the construction of enterostomies. Eight patients had a sigmoideostomy performed because of the combination of diarrhea and fecal incontinence, while one patient had intractable constipation and was judged to be in need of an ileostomy. Together with three patients who were reported earlier (VI) six new patients have been added. The mean age was 51.4 years (range 38 - 65) and the mean duration of the symptoms was 8.1 years (range 6 - 12) until the operation. In four patients the fecal incontinence had lasted less than one year until the operation was performed. Four of the operated patients are now dead, the time from operation until death ranged from two months to five years. The cause of death was not related to the operation per se in any case. The remaining five patients are still alive. No remarkable problems have been encountered as to the management of the ostomy and the appliances. The clinical details of the operated patients are outlined in Table III.

No effective causal treatment of FAP has yet been described. Some promising results, however, have been reported from the trials of Dimethylsulfoxide (DMSO). DMSO is a remarkable solvent, which has been reported to increase the solubility of amyloid fibrils (85). Localized skin application of DMSO was shown to increase the conduction velocity of the peroneal nerves in 3 out of 9 patients (7). Oral administration of DMSO was reported to achieve clinical improvement and to increase the excretion of low molecular weight protein in the urine (61). However, the patients are reluctant to take DMSO because of the strong foetor ex ore. No other serious side effects were noted.

Symptomatic therapy of the gastrointestinal syndrome of FAP is most often directed towards constipation, diarrhea, gastric retention and anal incontinence. Large doses of hydrophilic colloids and lactulose
have been fairly successful in combatting the constipation, but in a few cases it was very resistant to treatment (VI). The antidiarrhoeic treatment has in general not been very successful but the frequency and urgency have been affected to some extent by aluminium trihydroxide preparations (Phosphaluge®), diphenoxylate (Retardin®), and loperamide (Imodium®). The gastric retention has so far been treated with little success with metoclopramide (Primperan®). A combination of severe diarrhea and anal incontinence is a great problem for the patients. They are virtually unable to leave their homes and they have to have access to a toilet at all the times. Surgical diversion of the fecal stream through a sigmoideostomy has been very successful in several such cases. Two patients underwent this operation at a late stage and died within a few months. The main advantage of the operative procedures is to enable the patients to move freely, to travel and to have social contacts with friends and relatives. In the late stages of FAP when the patients are bedridden or admitted to some institution it facilitates the nursing. In spite of neuropathy of the hands the patients were able to cope with the ostomy appliances remarkably well.
Table III. Clinical details of nine patients with enterostomies.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age at operation</th>
<th>Sex</th>
<th>Family history</th>
<th>Duration until operation (yrs)</th>
<th>Duration of incontinence (yrs)</th>
<th>Degree of neuropathy at op.</th>
<th>Gastrointestinal symptom</th>
<th>Survival after op. (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.B.</td>
<td>42</td>
<td>F</td>
<td>Neg</td>
<td>9</td>
<td>None</td>
<td>3</td>
<td>Constipation</td>
<td>Alive 6</td>
</tr>
<tr>
<td>R.A.</td>
<td>46</td>
<td>M</td>
<td>Neg</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>Diarrhea</td>
<td>Alive 7</td>
</tr>
<tr>
<td>H.K.</td>
<td>53</td>
<td>M</td>
<td>Neg</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>Diarrhea</td>
<td>Alive 5</td>
</tr>
<tr>
<td>G.H.</td>
<td>58</td>
<td>F</td>
<td>Pos</td>
<td>12</td>
<td>2</td>
<td>4</td>
<td>Diarrhea</td>
<td>Dead 2/12</td>
</tr>
<tr>
<td>G.Q.</td>
<td>38</td>
<td>M</td>
<td>Pos</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>Diarrhea</td>
<td>Dead 5</td>
</tr>
<tr>
<td>S.M.</td>
<td>65</td>
<td>F</td>
<td>Pos</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>Diarrhea</td>
<td>Alive 2</td>
</tr>
<tr>
<td>H.P.</td>
<td>48</td>
<td>M</td>
<td>Neg</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>Diarrhea</td>
<td>Dead 2</td>
</tr>
<tr>
<td>E.J.</td>
<td>49</td>
<td>F</td>
<td>Neg</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>Diarrhea</td>
<td>Alive 2</td>
</tr>
<tr>
<td>N.H.</td>
<td>64</td>
<td>F</td>
<td>Neg</td>
<td>8</td>
<td>0</td>
<td>4</td>
<td>Bouts of diarrhea</td>
<td>Dead 5/12</td>
</tr>
</tbody>
</table>
GENERAL SUMMARY AND CONCLUSIONS

1. Gastrointestinal symptoms were found in 47 out of 52 patients. Diarrhea and constipation or both alternating were the most common complaints. There was a tendency for diarrhea to become increasingly frequent from the onset of gastrointestinal symptoms until the time of admission to this hospital. During the follow-up period all of 21 patients ultimately developed gastrointestinal symptoms and there was a high prevalence of diarrhea at the end of this period while only two patients had constipation. Symptoms of peripheral polyneuropathy usually preceded the gastrointestinal complaints. The symptoms from the gastrointestinal tract were probably mainly caused by a disruption of the autonomous nervous system of the gut.

2. On admission steatorrhea was found in 30 out of 52 patients and an impaired d-xylose absorption in 26 out of 50 patients. During the follow-up period there was a variability in the fecal fat output ranging from normal to high when it was determined several times in the same patient. Nineteen out of 21 patients displayed steatorrhea at some time during the follow-up. The peripheral polyneuropathy as expressed by emg-score and the duration at the follow-up study were both significantly correlated to the development of steatorrhea. The variations in the fecal fat output, its relationship to the emg-score and the lack of correlation to oral lactose and glucose tolerance tests indicate an intraluminal cause for steatorrhea and impaired d-xylose absorption which both are known to be caused by bacteria. This intraluminal factor may thus be bacterial overgrowth in the small intestine caused by an altered motility and gastric hypochlorhydria.

3. Increased bile acid deconjugation was demonstrated by means of bile acid breath test in 6 out of 13 investigated patients, of whom all 6 returned to normal values after one week of antibacterial treatment. Four out of 5 patients with initially impaired d-xylose absorption test in the group of patients with abnormal bile acid breath test were also normalized while the fecal fat output was only marginally
influenced. The results indicate strongly, however indirectly, that bile acid deconjugation due to bacterial overgrowth of the small intestine is an important causative factor for the gastrointestinal dysfunction in Familial Amyloidosis with Polyneuropathy.

4. The jejunal villous structure was normal in all cases and the degree of amyloid infiltration was not related to the symptomatic state, the fecal fat output or an impaired d-xylose absorption. The surface ultrastructure was also normal in all cases. These findings support the assumption that amyloid infiltration of the gut mucosa is probably not the major cause of the gastrointestinal dysfunction.

5. The radiographic studies of the stomach, the small intestine and the colon revealed no anatomical abnormalities specific for FAP. However, gastric retention was found in 7 out of 37 patients investigated. Gastroscopy fairly frequently revealed solid residues and aperistaltic antral-pyloric segments. The barium transit time did not correlate to fecal fat output or diminished d-xylose absorption. Defective gastric emptying, however, did correlate to a decreased d-xylose absorption but not to the fecal fat output.

6. There is no causal treatment for FAP. However, the situation for the patients may be improved substantially by diverting the fecal stream.
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