Familial Occurrence of Abdominal Aortic Aneurysms

by

ÖRJAN NORRGÅRD

Umeå University 1985
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ÖRJAN NORGÅRD

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ABSTRACT

The occurrence of clinically diagnosed and/or ruptured abdominal aortic aneurysms (AAAs) in the families of 220 patients with AAAs, treated at the Surgical Clinic, University Hospital of Umeå in the northern part of Sweden during the years 1965-82, was studied. A questionnaire concerning the blood relatives was answered by 87/89 patients.

16/87 patients (18%) had blood relatives with AAAs. In 14 families one blood relative was affected, and in 2 families two blood relatives were affected. First degree relatives were affected in 9/87 cases (10%), and second degree relatives in 7/87 cases (8%). 9/468 (1.9%) of the patients' brothers and sisters but only five of all their cousins had AAAs, and 7/204 (3.4%) of the dead brothers and sisters had died of ruptured AAAs. Concerning the patients who were not included in the letter survey at least 14/133 had blood relatives with AAAs. However, the great majority of these patients were dead when the study was performed and could not be asked about the occurrence of AAAs in their families.

The patients with AAAs had significantly higher serum concentrations of triglyceride and (VLDL + LDL)-cholesterol and a significantly lower serum concentration of HDL-cholesterol than randomly selected healthy controls of the same sex and age as the patients.

We also compared the distributions of genetic markers (HLA antigens, the blood group systems ABO, Rh, MNSs, P, Kell, Lewis and Duffy and the serum protein group systems haptoglobin, transferrin, group-specific component, complement C3, properdin factor and alpha-1-antitrypsin) in patients with AAAs with the distributions in controls and in some cases with the expected distributions according to the Hardy-Weinberg law. A significantly decreased frequency of Rh-negative individuals, and significantly increased frequencies of Kell-positive individuals, of MN heterozygotes and of heterozygotes concerning haptoglobin type was found.

Furthermore, the aneurysm walls of patients with and without AAAs in the family were compared concerning the morphology, but no differences were found. We also studied the occurrence of collagen types I and III in the aneurysm walls, and the occurrence of vimentin and desmin in the smooth muscle cells of the aneurysm walls, but all these components were present in the aneurysm walls of both the patients with and those without AAAs in the family.

To summarize the results, there seems to be an increased frequency of AAAs, and especially of ruptured AAAs, among the brothers and sisters of patients with AAAs. Elevated serum concentrations of triglyceride and (VLDL + LDL)-cholesterol and a lowered serum concentration of HDL-cholesterol seems to be common in patients with AAAs. There seems to be a hereditary predisposition to the development of AAAs, because we found associations with four different genetic markers (Rh, MN, Kell, haptoglobin group). However, there is probably no specific "familial" type of AAAs, because we found no differences between the patients with and those without AAAs in the family.

Key words: Abdominal aortic aneurysms, familial occurrence, serum lipids and lipoproteins, genetic markers, morphology, collagen types, vimentin, desmin.
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The patients with AAAs had significantly higher serum concentrations of triglyceride and (VLDL + LDL)-cholesterol and a significantly lower serum concentration of HDL-cholesterol than randomly selected healthy controls of the same sex and age as the patients. We also compared the distributions of genetic markers (HLA antigens, the blood group systems ABO, Rh, MNSs, P, Kell, Lewis and Duffy and the serum protein group systems haptoglobin, transferrin, group-specific component, complement C3, properdin factor and alpha-1-antitrypsin) in patients with AAAs with the distributions in controls and in some cases with the expected distributions according to the Hardy-Weinberg law. A significantly decreased frequency of Rh-negative individuals, and significantly increased frequencies of Kell-positive individuals, of MN heterozygotes and of heterozygotes concerning haptoglobin type was found.

Furthermore, the aneurysm walls of patients with and without AAAs in the family were compared concerning the morphology, but no differences were found. We also studied the occurrence of collagen types I and III in the aneurysm walls, and the occurrence of vimentin and desmin in the smooth muscle cells of the aneurysm walls, but all these components were present in the aneurysm walls of both the patients with and those without AAAs in the family.

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Key words: Abdominal aortic aneurysms, familial occurrence, serum lipids and lipoproteins, genetic markers, morphology, collagen types, vimentin, desmin.
To Eivor and Erik
ABBREVIATIONS

AAA = abdominal aortic aneurysm
FAAA = familial abdominal aortic aneurysm
ICA = intracranial aneurysm
VLDL = very low density lipoproteins
LDL = low density lipoproteins
HDL = high density lipoproteins

Pedigree = family tree
Proband = the individual from which the study of a specific family originates
This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I Norrgård Ö, Rais O, Ängquist KA.  
Familial occurrence of abdominal aortic aneurysms.  

II Norrgård Ö, Ängquist KA, Johnson O.  
Familial aortic aneurysms-serum concentrations of triglyceride, cholesterol, HDL-cholesterol and (VLDL + LDL)-cholesterol.  
Brit J Surg, Accepted for publication, August 1984.

III Norrgård Ö, Cedergren B, Ängquist KA, Beckman L.  
Blood groups and HLA antigens in patients with abdominal aortic aneurysms.  

IV Norrgård Ö, Fröhlander N, Beckman G, Ängquist KA.  
Association between haptoglobin groups and aortic abdominal aneurysms.  

V Thornell L-E, Norrgård Ö, Eriksson A, Vanderwee M, Ängquist KA.  
Submitted for publication
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INTRODUCTION

Arterial aneurysms were described already in the Eber Papurys in 1550 B.C. (1). In the second century A.D., Galen described an aneurysm as "a pulsative swelling, from which bright blood spurted with great violence if it was wounded" (2). Antyllus, in the same century, distinguished between true and false aneurysms. He wrote: "There are two kinds of aneurysms, the one where there is a local dilatation of the artery, and the other from a rupture of the artery and discharge of blood to the flesh beneath it. Aneurysms due to dilatation are longer than the others. Those due to rupture are rounder" (3). According to Aetius of Amida, in the 6th century A.D., the most common localization of aneurysms was on the neck, but aneurysms of the brachial artery caused by unskilled phlebotomy were also common (3). In 1567, Vesalius of Brussels described an abdominal aortic aneurysm (AAA), and in the same century Ambroise Paré suggested, that aneurysms could be caused by lues (3).

Already in Galen's and Antyllus' days, false aneurysms on the extremities had been treated by ligation of the artery (3). The first operation on the aorta was performed by Sir Astley Cooper in 1817, when he ligated the abdominal aorta of a patient with a leaking aneurysm of the iliac artery (4, 5). However, the patient died postoperatively. The first successful ligation of the abdominal aorta was performed by Rudolph Matas in 1923 (4-6). His patient had an AAA. During the following years a few patients with AAAs were operated on by ligation of the abdominal aorta, or by alternative methods such as wrapping and wiring, but the results were very discouraging (4, 5, 7). However, a new era in the treatment of AAAs started after 1951, when Dubost performed the first successful resection of an AAA with restitution of the continuity through a homologous graft (8). Within a short period of time, others had successfully performed the same type of operation, and within a few years synthetic grafts had replaced the homografts in this type of operation (9-11).

The operative mortality at elective operations of AAAs has progressively decreased during the past 30 years, and now varies between 1% and 10% in different studies, while the operative mortality at emergency
operations still is about 40% (12-15). The real mortality in ruptured AAAs is higher, because some of these patients die before they come to the operating theatre.

The number of elective operations for AAAs has increased, and this depends upon the good results at elective operations and the high risk that AAAs will rupture (12, 16, 17). However, the real frequency of AAAs in industrial countries has probably also increased during this century. According to Kampmeier in a study from 1936, only 313 AAAs had been reported in the literature, and he added 68 cases found among the 215,516 patients admitted to the Charity Hospital during a 30-year period (18). In autopsy studies from the same period the frequency of patients with AAAs varied between 0.2% and 0.5%, while in autopsy studies from the 1960s and the 1970s the frequency varied between 1% and 6% (18-23). However, many of the AAAs found in the autopsy studies were small, and the majority of them had not been diagnosed clinically and had not ruptured.

Not only the frequency but also the etiology of AAAs has changed during this century. In the great majority of the studies performed before 1950 nearly all the AAAs were considered to be caused by lues, while in later studies nearly all of them were considered to be caused by atherosclerosis (18-24). However, it has been pointed out that the change in etiology was very abrupt, and that some of the AAAs in the earlier studies probably were caused by atherosclerosis instead of lues (19).

It is not known, why only a small fraction of all the individuals with atherosclerosis of the abdominal aorta develops AAAs, and why another small fraction develops luminal occlusion of the abdominal aorta rather than an aneurysm (25, 26). It has been suggested, that other factors than atherosclerosis also contribute to the development of atherosclerotic AAAs (27-29).

Mycotic AAAs and AAAs caused by noninfectious arteritis are uncommon in western countries today (30, 31). AAAs have also been reported in a few patients with rare hereditary connective tissue disorders, such as Marfan's and Ehlers-Danlos' syndromes (32, 33).
In the present investigation we have studied the frequency of familial aggregation of atherosclerotic AAAs, and the pattern of the familial aggregation of AAAs. The only report on this subject that we had found in the literature was a case report from Great Britain presented by Clifton in 1977 (34). He wrote about a family, in which all the three children had developed atherosclerotic AAAs when they were between 60 and 70 years old. All of them were men, and there were no history of hereditary connective tissue disorders in their family.

Concerning familial aggregation of non-atherosclerotic AAAs, Massumi et al reported in 1967 about two twins, a man and a woman, with Marfan's syndrome, who had clinically diagnosed AAAs (35). However, both of them died in ruptured thoracic aortic aneurysms. The female twin died at the age of 35 during pregnancy, and the male twin died at the age of 30.

The influence of hereditary factors for the development of AAAs was also studied by us. Patients with AAAs were studied concerning the serum concentrations of lipids and lipoproteins and concerning the distributions of some genetic markers.

The serum concentrations of lipids and lipoproteins are of interest because atherosclerosis is probably involved in the development of AAAs (21, 22, 24-28). In atherosclerotic diseases of the coronary arteries it has been shown that important risk factors are high serum concentrations of total cholesterol and LDL-cholesterol, and a low serum concentration of HDL-cholesterol (36, 37). These serum concentrations are to some extent genetically determined, and this may partly explain the predisposition to coronary artery disease in some families (38-40). Concerning patients with AAAs, we had found only two studies in which the serum concentrations of triglyceride and cholesterol were reported (41, 42). In one of them both the serum concentrations of triglyceride and total cholesterol were higher in the patients than in the controls (41). In the same study hyperlipoproteinaemia according to Fredrickson was reported, and 36% of the patients had abnormal lipoprotein patterns.

The studied genetic markers were HLA antigens, the blood group systems ABO, Rh, MNSs, P, Kell, Lewis, and Duffy, and the serum protein group
systems haptoglobin (Hp), transferrin (Tf), group-specific component (Gc), complement C3, properdin factor (Bf), and alpha-1-antitrypsin (Pi).

Concerning these markers there are very few studies in patients with AAAs. There are four studies about ABO blood groups (43-46) and one study about Rh blood groups (47). In one of the studies concerning ABO blood groups a significant increase of blood group A was found (45), and in the study concerning Rh blood groups a significant increase of Rh-negative individuals was found (47).

In the present investigation the morphology of the aneurysm walls of patients with and without AAAs in the family was also studied. The morphology studied by conventional histology has been described in other studies (26-28, 48). Since collagen is a major strengthening component of the wall of the abdominal aorta (29, 48, 49), and it has been reported that some patients with intracranial aneurysms are deficient in collagen type III (50), we also studied the occurrence of collagen types I and III in the aneurysm walls. We also compared the smooth muscle cells of the abdominal aorta in individuals with and without AAAs, and in patients with and without AAAs in the family. The reason was that the smooth muscle cells are considered to produce the strengthening components of the aortic wall (27, 51-53). The comparison of the aortic smooth muscle cells was performed by studying the occurrence of vimentin and desmin in the intermediate filament components (54, 55). It has been reported that only vimentin-containing smooth muscle cells are present in experimentally induced intimal thickening in the rat, while both vimentin- and desmin-containing smooth muscle cells are present in the normal aortic intima of the rat (54).

AIMS OF THE INVESTIGATION

The aims of this investigation were
- to estimate how often patients with AAAs have blood relatives with the same disease, and to estimate the frequency of individuals with AAAs among the blood relatives of patients with AAAs (I),
- to study the pattern of the familial aggregation of AAAs (I),
- to compare the serum concentrations of lipids and lipoproteins in patients with "familial" and "non-familial" AAAs and in healthy controls (II),
- to compare the distributions of different genetic markers in patients with "familial" and "non-familial" AAAs and in controls (III, IV),
- to study the morphology of the aneurysm walls with conventional histology, enzyme histochemistry and immunohistochemistry with antibodies against collagen types I and III, vimentin and desmin (V).

MATERIAL AND METHODS

This investigation comprised 220 patients with AAAs, treated at the Surgical Clinic, University Hospital of Umeå in the northern part of Sweden, during the years 1965-82. It includes all the patients treated during the years 1965-81 and 20 of the patients treated in 1982. However, there were different numbers of patients in the different studies, and there were differences between the patients in different studies concerning the mean age at the time of diagnosis and where the patients lived. A summary of the different groups of patients is given in Table I.

In all there were 172 men and 48 women. The mean age of the patients at the time of diagnosis was 66.9 years (SD ± 8.8 years, range 44-90 years). Six patients were younger than 50 years and 13 patients were older than 80 years. The mean age of the men was 66.1 years (SD ± 8.8 years) and the mean age of the women was 70.2 years (SD ± 8.0 years). This difference is statistically significant (t218=2.9, p<0.01).

There were 127 elective cases and 93 emergency cases. Concerning the emergency cases, 30 aneurysms were leaking and 63 had ruptured. The rupture was retroperitoneal in 36 cases and into the abdominal cavity in 27 cases. In the great majority of cases the aneurysms had been visualized on roentgenograms of the abdomen. Furthermore, the diagnosis had been confirmed by aortography in all the elective cases and in 37 emergency cases. Elective operations had been performed in 87 cases and emergency operations in 66 cases. In 27 cases, patients with ruptured
Table I. Number of patients, mean age at the time of diagnosis and home county of the patients in the different studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Patients with AAA in the family</th>
<th>Mean age at the time of diagnosis</th>
<th>County Västerbotten</th>
<th>County Norrbotten</th>
<th>County Västerbodenland</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Patients with AAA in the family</td>
<td>Men</td>
<td>Women</td>
<td>Västerbotten</td>
<td>Norrbotten</td>
</tr>
<tr>
<td>Total material</td>
<td>220</td>
<td>30</td>
<td>172</td>
<td>48</td>
<td>66.9 ± 8.8</td>
<td>124</td>
</tr>
<tr>
<td>Study I</td>
<td>89</td>
<td>16</td>
<td>70</td>
<td>19</td>
<td>63.5 ± 8.4</td>
<td>46</td>
</tr>
<tr>
<td>Deceased patients</td>
<td>111</td>
<td>11</td>
<td>85</td>
<td>26</td>
<td>69.6 ± 8.3</td>
<td>69</td>
</tr>
<tr>
<td>Study II</td>
<td>51</td>
<td>18</td>
<td>38</td>
<td>13</td>
<td>63.6 ± 8.2</td>
<td>34</td>
</tr>
<tr>
<td>Lipids and lipoproteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study III</td>
<td>117</td>
<td>29</td>
<td>93</td>
<td>24</td>
<td>65.2 ± 9.0</td>
<td>55</td>
</tr>
<tr>
<td>ABO and Rh blood groups</td>
<td></td>
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<td></td>
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<tr>
<td>Study III, IV</td>
<td>55</td>
<td>17</td>
<td>40</td>
<td>15</td>
<td>63.3 ± 8.3</td>
<td>39</td>
</tr>
<tr>
<td>Genetic markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study V</td>
<td>24</td>
<td>5</td>
<td>22</td>
<td>2</td>
<td>67.9 ± 5.9</td>
<td>8</td>
</tr>
<tr>
<td>Walls of aneurysms</td>
<td></td>
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</tr>
</tbody>
</table>
AAAs had died preoperatively or at the beginning of the operation, but the diagnosis of these patients was confirmed at autopsy.

The patients came in 124 cases from our own county, the county Västerbotten (population 236,000), in 59 cases from the county of Norrbotten (population 264,000) and in 37 cases from the northern part of the county of Västernorrland (population 146,000). Patients had been referred from all the 11 other hospitals in the area of the university hospital. Concerning our own county, 87/124 patients came from the primary area of the university hospital (population 110,000). The large number of patients from the primary area of the university hospital in relation to the population depends upon, that many patients had been treated at district hospitals and county hospitals.

As illustrated in Table I, there are differences between the patients in the different studies concerning the mean age at the time of diagnosis and concerning home county of the patients. The mean age of the patients in some of the studies was lower than the mean age of the patients who were not included in the study. This depends on that these studies were retrospective concerning the patients treated before 1982, and many patients who were old when their aneurysms had been diagnosed had already died when our studies were performed. In studies II, III and IV, the proportion of patients from the county of Västerbotten was higher than in the other studies, because in the retrospective group, for practical and economical reason, we only tried to obtain blood samples from the patients from our own county. However, concerning the patients with AAAs in the family, we tried to obtain blood samples from all of them irrespective of where they lived. All the controls in studies II-IV came from our own county.

The patients who were treated in 1982, and included in the investigation, were interviewed about the occurrence of AAAs in their families when they arrived to the hospital. All these patients except one had been treated electively.
Study I
The aims were to study the frequency of familial occurrence of AAAs, and the pattern of the familial aggregation of AAAs.
The study was retrospective and comprised all the 200 patients with AAAs treated at the clinic during the years 1965-81. However, only 89 of these patients were still alive when the study was performed. A letter survey concerning the occurrence of AAAs in the family was conducted among the patients who were still alive, while information about the families of the deceased patients was obtained from the medical records.

At the time of diagnosis the mean age of the patient who were still alive was 63.5 years (SD ± 8.4 years), while the mean age of the remaining patients was 69.6 years (SD ± 8.3 years). The difference is statistically significant (t_{198} = 5.1, p < 0.001). In 115 cases (57.5%) the patients came from the county of Västerbotten.

Study II
The aim was to compare the serum concentrations of triglyceride, total cholesterol, (VLDL + VLD)-cholesterol and HDL-cholesterol in AAA-patients with and without AAAs in the family and in healthy controls.

This study comprised 51 patients, 38 men and 13 women, of whom 37 had been treated before 1982. Therefore, the mean age of the patients was lower than the mean age of the rest of the patients at the time of diagnosis (63.6 ± 8.2 years and 68.3 ± 8.3 years respectively, t_{218} = 3.59, p < 0.001). In 34 cases (66.7%) the patients came from the county of Västerbotten. Twelve patients had first degree relatives (brothers, sisters and/or parents) with AAAs, and six patients had second degree relatives (cousins or brothers and sisters of the parents) with AAAs.

As controls served 51 of the randomly selected participants in a population study of serum lipids. They had been matched with our patients concerning sex and age. However, there were no individuals in the population study of the same age as the oldest patients, and in these cases the oldest available controls were selected. Consequently, the mean age of the patients was higher than the mean age of the controls.
when the blood samples were obtained (66.7 ± 7.4 years and 63.8 ± 5.5 years respectively, $t_{100} = 2.23$, $p < 0.05$).

In the patients HDL-cholesterol was determined on serum samples after precipitation of VLDL and LDL by heparin-manganese precipitation, while in the controls the precipitation had been done after ultracentrifugal removal of VLDL. However, there was an excellent agreement between the two methods.

**Studies III and IV**

The aim was to compare the distributions of genetic markers in AAA-patients with the distributions in controls and, in some cases, with the expected distribution according to the Hardy-Weinberg law (56). In study III, the genetic markers studied were HLA antigens A and B and the blood group systems ABO, Rh, MNSs, P, Kell, Lewis and Duffy, and in study IV the serum protein groups haptoglobin (Hp), transferrin (Tf), group-specific component (Gc), complement C3, properdin factor (Bf) and alpha-1-antitrypsin (Pi) were studied.

The frequencies of ABO and Rh blood groups were based upon the routinely performed typings of 117 patients, 93 men and 24 women. In 29 cases the patients had AAAs in their families. However, in four cases two brothers and sisters and in three cases two cousins with AAAs had been typed, and therefore the 29 patients with AAAs in the family were of 22 different families.

Concerning the other genetic markers, blood samples were obtained from 55 patients, 40 men and 15 women, of whom 17 had blood relatives with AAAs. The diseased family member was in 11 cases a first degree relative and in six cases a second degree relative. The blood samples had in 41 cases been obtained from patients who had been treated before 1982, and therefore the mean age of the patients studied was lower than the mean age of the remaining patients at the time of diagnosis (63.3 ± 8.3 years and 68.4 ± 8.3 years respectively, $t_{218} = 3.9$, $p < 0.001$). The patients in 39 cases (70.9%) came from the county of Västerbotten.
The typing for HLA antigens and blood groups was performed at the Blood Center in Umeå and the typing for serum protein groups at the Department of Medical Genetics in Umeå.

Subjects from the county of Västerbotten, who had already been typed for other reasons served as controls. In some cases these subjects had participated in other studies performed at the Department of Medical Genetics in Umeå (57-60), and in other cases (i.e. Bf, Gc, Pi) the results of the typings were available at the same institution but not published yet.

Study V
The aim of this study was to compare the aneurysm walls of patients with and without AAAs in the family concerning morphology studied by conventional histology, enzyme histochemistry and immunohistochemistry with antibodies against collagen types I and III, vimentin and desmin.

The study comprised 24 patients, 22 men and 2 women, operated on for AAAs at the Surgical Clinic, University Hospital of Umeå during the years 1981 and 1982. Five patients had blood relatives with AAAs, and one patient had both an AAA and an intracranial aneurysm (ICA). Subjects without aortic disease, who had been autopsied at the State Institute of Forensic Medicine in Umeå, served as controls.

A ring of the circumference at the cranial border of the aneurysm was taken as a biopsy during the operations, and from the controls the corresponding part of the abdominal aorta was taken at autopsy. Cryostat sections from all the aortic specimens were stained for conventional histology and enzyme histochemistry, while cryostat sections from ten patients were stained for collagen types and cryostat sections from 12 patients for vimentin and desmin.

Concerning the collagen study two of the patients with AAAs in the family and the patient with both an AAA and an ICA were included, and concerning the vimentin and desmin studies all five patients with AAAs in the family and the patient with both an AAA and an ICA were included.
Statistical methods
Student's t-test was used to test the difference in ages between the patients in different groups.

The chi-square test was used to compare the numbers of patients and controls in different alternative groups, and to compare the observed and the expected numbers of patients in alternative groups. Yates correction for continuity was used when the number of patients was small (61).

The expected numbers of patients with alternative phenotypes, for example blood groups MM, MN and NN, was calculated according to the Hardy-Weinberg law (56). The gene frequencies $p$ and $q$ of the genes M and N in this example were calculated from the observed numbers of patients with the alternative phenotypes, and these gene frequencies were used to calculate the expected numbers of patients with alternative phenotypes. If there are $n_1$ MM-individuals, $n_2$ MN-individuals and $n_3$ NN-individuals, the gene frequencies $p$ and $q$ are:

$$p = \frac{2n_1 + n_2}{2(n_1 + n_2 + n_3)}$$

and

$$q = 1 - p.$$

The expected numbers of individuals with the alternative phenotypes will be: $p^2(n_1 + n_2 + n_3)$ MM-individuals, $2pq(n_1 + n_2 + n_3)$ MN-individuals and $q^2(n_1 + n_2 + n_3)$ NN-individuals.

The Mann-Whitney U-test was used to test the difference between two groups concerning the serum concentrations of lipids and lipoproteins in study II (62).

Only two-tailed tests were used, and p-values below 0.05 were considered to be statistically significant.

RESULTS

Familial occurrence of AAAs (I)
A detailed presentation of the results concerning the patients treated before 1982 is given in Study I. The results of that study are summarized here and in addition, the results concerning the patients treated in 1982 are presented.
The letter survey. The questionnaire was answered by 87/89 patients. Sixteen patients responded, that they had blood relatives with AAAs, but this information was wrong in three cases. In one case a sister of the patient had a thoracic aortic aneurysm instead of an AAA, and in the two other cases the patient's blood relatives had no aneurysms at all. On the other hand, at least three of the patients who denied that there were any AAAs in their families had blood relatives with AAAs. In these cases we suspected that we had obtained wrong information from the patients, because they had the same surnames and came from the same communities as three other patients with AAAs, who had been treated at our clinic earlier.

Thus, at least 16/87 patients (18%) had blood relatives with AAAs. In 14 families there was only one blood relative with AAA, and in two families there were two blood relatives with AAAs. In one of these two cases both the patient's father and one of his two brothers had died of ruptured AAAs, and in the other both a brother and a sister of the patient's father had died of ruptured AAAs.

Nine out of 87 patients (10%) had first degree relatives with AAAs, and 7/87 patients (8%) had second degree relatives with AAAs. In 9/468 cases (1.9%) the patients' brothers and sisters were affected, and 7/204 or 3.4% of the dead brothers and sisters had died of ruptured AAAs.

Among the blood relatives 14/18 (78%) of the AAAs had ruptured, while only 92/200 (46%) of the AAAs treated at our clinic during the years 1965-81 had ruptured or were leaking.

In the 16 families with more than one AAA, there were 34 subjects with AAAs, of whom 28 were men and 6 were women. In the remaining families, there were 55 men and 16 women with AAAs. There was no difference between the two groups concerning the proportions of men and women.

At the time of diagnosis the mean age of the 16 patients with AAAs in the family was 64.3 years (SD ± 7.8 years), while the mean age of the remaining 71 patients was 63.4 years (SD ± 8.6 years).

Concerning the 16 families with more than one AAA, two came from Vittangi and two from Övertorneå, which are very small communities in
the northern part of the area served by the university hospital. However, there was no consanguinity in these or in the other families. A more detailed description of where 216 of the patients in the investigation came from is given in Fig. I.

The deceased patients. According to the medical records four of these 111 patients, of which two were sisters, had AAAs in the family. However, there were at least seven other patients with AAAs in the family. This information was obtained by mere chance, because the patients were of the same families as seven of the patients who had answered the questionnaire.

Each of the eleven patients with AAAs in the family had at least one blood relative with AAA. The diseased family member was in eight cases a first degree relative and in three cases a second degree relative.

The patients treated in 1982. Twenty of the patients treated in 1982 were interviewed about the occurrence of AAAs in their families, and 3/20 patients had blood relatives with AAAs. The diseased family member was in one case the patient's mother, in one case one of the patient's two sons and in one case a brother of the patient. Pedigrees of these three new families with more than one AAA are shown in Fig. II.

The total number of families with more than one AAA in the different parts of this study was 22. In 20 of these families there were two individuals with AAAs, and in two families there were three individuals with AAAs, including the probands. The diseased family member was in 15 families a first degree relative and in 7 families a second degree relative. Concerning the 15 patients with AAAs among the first degree relatives, 13 patients had brothers and sisters with AAAs, while the patient's father was affected in one case and one of the patient's sons in another. Concerning the seven patients with AAAs among the second degree relatives, five patients had cousins with AAAs.

AAAs and ICAs (I)

Before the letter survey was conducted we already knew that one of our patients had blood relatives with ICAs. Therefore the patients in the letter survey were also asked about the occurrence of ICAs in their
Fig. I. Home communities of 216 of the AAA-patients. The map shows the area served by the university hospital in Umeå.
Fig. II. The families of the three patients with AAAs in the family, who had been treated in 1982 (square = male, circle = female, arrow under the symbol = proband, black symbol = AAA).

families. At least 5/87 of the patients had blood relatives with ICAs. In one case both a brother and a sister of the patient had died of ruptured ICAs, and a cousin of the same patient had been operated on for an AAA. In another case a sister of the patient's mother had died of a ruptured ICA, and a brother of the patient had an AAA. Concerning the remaining patients, two had a brother with an ICA and one had a cousin with an ICA.

Furthermore, 2/87 patients in the letter survey had ICAs themselves. One of them had already been operated on for an ICA when he was treated at our clinic, and the other patient has recently died of a ruptured ICA. There were no AAAs or ICAs in the families of these two patients.

Lipids and lipoproteins (II)
The serum concentrations of lipids and lipoproteins in patients and in controls are presented in detail in Table II of Study II, while the proportion of tobacco smokers and the occurrence of other atherosclerotic diseases are given in Table I of the same study.

Concerning the smoking habits, 40/51 patients and 14/51 controls were smokers. The difference is statistically significant ($X^2=26.6$, 1 d.f., $p < 0.001$).
Twenty out of 51 patients had coronary artery disease, 8/51 patients suffered from intermittent claudication and 2/51 patients had had transient ischaemic attacks. More than one of these diseases occurred in some of the patients, and the total number of patients with at least one disease was 25/51.

The serum concentration of triglyceride was higher in the 38 male patients than in the 38 male controls (1.61 ± 0.10 mmol/l and 1.24 ± 0.10 mmol/l, respectively, U = 722, p < 0.01), and also in the 13 female patients compared to the 13 female controls (1.96 ± 0.29 mmol/l and 1.26 ± 0.12 mmol/l, respectively, U = 39, p < 0.05).

Concerning the serum concentration of total cholesterol, there was no statistically significant difference between the male patients and the male controls or between the female patients and the female controls.

The serum concentration of HDL-cholesterol was lower in the male patients than in the male controls (1.01 ± 0.04 mmol/l and 1.60 ± 0.05 mmol/l, respectively, U = 132, p < 0.001), and again in the female patients compared to the female controls (1.22 ± 0.13 mmol/l and 1.96 ± 0.15 mmol/l, respectively, U = 26, p < 0.01).

The serum concentration of (VLDL + LDL)-cholesterol was higher in the male patients than in the male controls (6.52 ± 0.35 mmol/l and 5.23 ± 0.23 mmol/l, respectively, U = 444, p < 0.01), and in the female patients compared to the female controls (6.48 ± 0.47 mmol/l and 5.20 ± 0.35 mmol/l, respectively, U = 41, p < 0.05).

No statistically significant differences were found between the patients with and those without AAAs in the family concerning the serum concentrations of lipids and lipoproteins.

Sixteen out of 38 men and 9/13 women had other atherosclerotic diseases. However, there was no difference between the men with and those without other atherosclerotic diseases, or between the women with and those without other atherosclerotic diseases, concerning the serum concentrations of triglyceride, total cholesterol, HDL-cholesterol and (VLDL + LDL)-cholesterol.
Genetic markers - HLA antigens and blood groups (III)

The results are presented in detail in Study III.

HLA antigens. A complete typing of seven HLA-A antigens and eleven HLA-B antigens was performed on 48 patients. No statistically significant differences were found between the patients and the 368 controls concerning the frequencies of these antigens.

ABO and Rh blood groups. The frequencies of ABO and Rh blood groups in 117 patients and in 59,862 controls were compared. The frequency of blood group A among the patients and the controls was 51.3 and 44.2% respectively, but this difference was not statistically significant. However, concerning Rh blood groups only 7.7% of the patients compared to 14.9% of the controls were Rh-negative ($X^2 = 4.79$, 1 d.f., $p < 0.05$). There were no statistically significant differences between the patients with and those without AAAs in the family concerning ABO and Rh blood groups.

MNSs blood groups. MN and Ss are separate blood group systems, but combinations of the two blood group systems are usually inherited as units (63). The frequencies of the MNSs blood groups in 54 patients and in 287 controls were compared.

Concerning the MN blood groups there was a statistically significant excess of MN heterozygotes among the patients compared with the expected number according to the Hardy-Weinberg law (56). The observed distribution was 16 MM-patients, 33 MN-patients and 5 NN-patients, while the expected distribution was 19.4 MM-patients, 25.9 MN-patients and 8.6 NN-patients ($X^2 = 4.08$, 1 d.f., $p < 0.05$). The frequencies $p$ and $q$ of the M- and N-genes among the patients were 0.6 and 0.4 respectively.

The departure from the Hardy-Weinberg equilibrium with an excess of MN heterozygotes was particularly pronounced among the 25 individuals who were ss homozygous. The observed distribution was 2 MM-patients, 19 MN-patients and 4 NN-patients, while the expected distribution was 5.3 MM-patients, 12.4 MN-patients and 7.3 NN-patients ($X^2 = 7.02$, 1 d.f., $p < 0.01$). 33/54 patients (61.1%) and 137/287 controls (47.7%) were MN-heterozygotes, but this difference was not statistically significant.
However, the MNss type was more common among the patients than among the controls (19/54 or 35.2% and 55/287 or 19.2% respectively, $X^2 = 6.87$, 1 d.f., $p < 0.01$). The frequencies $p$ and $q$ of the M- and N-genes among the controls were 0.58 and 0.42, respectively.

Concerning the 17 patients with familial AAAs, there was also a statistically significant departure from the Hardy-Weinberg equilibrium with an excess of MN-heterozygotes. The observed distribution was 2 MM-patients, 13 MN-patients and 2 NN-patients, while the expected distribution was 4.3 MM-patients, 8.5 MN-patients and 4.3 NN-patients ($X^2 = 4.76$, 1 d.f., $p < 0.05$). The gene frequencies $p$ and $q$ were 0.5. The frequency of MN-heterozygotes among these patients was also higher than among the controls (13/17 or 76.5% and 137/287 or 47.7%, respectively, $X^2 = 4.23$, 1 d.f., $p < 0.05$, Yates correction).

Concerning the Ss blood groups there was no statistically significant deviation from the Hardy-Weinberg equilibrium, and no statistically significant difference between the patients and the controls.

**Kell blood groups.** The distributions in 54 patients and in 2,164 controls were compared.

There was a higher frequency of Kell-positive individuals among the patients than among the controls (7/54 or 13% and 83/2,164 or 3.8% respectively, $X^2 = 8.82$, 1 d.f., $p < 0.005$, Yates correction). However, there was only one Kell-positive individual among the 17 patients with AAAs in the family.

**Lewis, Duffy and P blood groups.** Concerning these blood groups there were no statistically significant differences between the patients and the controls.

The frequencies of the Lewis blood groups among the 52 patients were 21.2% a+b−, 75% a−b+ and 3.8% a−b−, and among the 265 controls 21.1% a+b−, 67.2% a−b+, 11.7% a−b−. Concerning the 17 patients with AAAs in the family there were 3 a−b+, 13 a−b+ and 1 a−b−.
The frequencies of the Duffy blood groups were among the 52 patients 29.6% $a^+b^-$, 37% $a^+b^+$ and 33.3% $a^-b^+$, and among the 797 controls 18.2% $a^+b^-$, 49.9% $a^+b^+$ and 31.9% $a^-b^+$.

Concerning the 17 patients with AAAs in the family there were 6 $a^+b^-$, 8 $a^+b^+$ and 3 $a^-b^+$.

The frequencies of the P blood groups were among the 53 patients 69.8% $P_1$ and 30.2% $P_2$, and among the 404 controls 76.2% $P_1$ and 23.8% $P_2$.

Concerning the 17 patients with AAAs in the family there were 12 $P_1$ and 5 $P_2$.

Genetic markers - serum protein groups (IV)

Haptoglobin (Hp) groups. The distributions of the haptoglobin groups in 55 patients and in 2,297 controls are shown in Table I of study IV. There was a statistically significant excess of Hp 2-1 heterozygotes among the patients compared with the controls and compared with the expected number of heterozygotes according to the Hardy-Weinberg law (56). The observed distribution was 4 type 1-1, 36 type 2-1 and 15 type 2-2, while the expected distribution was 8.8 type 1-1, 26.4 type 2-1 and 19.8 type 2-2 ($X^2 = 7.27, 1$ d.f., $p < 0.01$). The frequencies $p$ and $q$ of the genes $Hpl$ and $Hp2$ were 0.4 and 0.6, respectively.

Concerning the 17 patients with AAAs in the family there were 12 type 2-1 and 5 type 2-2, while the expected numbers were 2.1 type 1-1, 7.7 type 2-1 and 7.2 type 2-2. The difference was not statistically significant ($X^2 = 3.341, 1$ d.f., $0.1 < p < 0.05$, Yates correction).

Transferrin (Tf), group specific component (Gc), complement C3, properdin factor (Bf) and alpha-1-antitrypsin (Pi). The results concerning these serum protein groups are presented in Table I of Study IV. There were no statistically significant differences between the patients and the controls concerning the distributions of these serum protein groups.

Aneurysm walls - morphology (V)

Conventional histology and enzyme histology. There were considerable differences between the aortic specimens from different patients con-
cerning the degrees of intimal, medial and adventitial changes. The intima was in most cases thickened with prominent atherosclerotic plaques, atheromas and ulcerations. Calcium deposits and elongated narrow spaces which had harboured cholesterol crystals were common. The media was in most cases thinner than normal, and the lamellar pattern was usually more or less destroyed with fragmentation and separation of the elastin fibers, and in some cases there were practically no elastin fibers at all. Concerning the adventitia connective tissue proliferation was common, and in some cases there was focal round cell reaction.

Long slender cells were common in the thickened intima and such cells also surrounded the atherosclerotic plaques. They stained both with NADH-TR and ATPase. In the media there was in most cases a decreased number of smooth muscle cells, which stained with both NADH-TR and APase. In the adventitia the smooth muscle cells of the vasa vasorum stained both with NADH-TR and ATPase, while the lymphoid cells stained only with NADH-TR.

There were no systematic differences between the aneurysm walls from patients with AAAAs in the family and those without.

**Immunohistochemistry - collagen types I and III.** The intima, the media and the adventitia of all the aneurysm walls stained both with antibodies against collagen types I and III. However, the specific staining of the media was in most cases more or less overshadowed by the strongly autofluorescent elastin fibrils. No differences could be demonstrated between patients with and without AAAAs in the family concerning the occurrence of collagen in the aneurysm walls.

**Immunohistochemistry - vimentin and desmin.** In the normal controls vimentin was present in the endothelial, the subendothelial and the medial cells, while desmin was present in only a few of the subendothelial cells and in a few of the cells in the outer part of the media. All the cells which contained desmin also contained vimentin. In the adventitia the bundles of smooth muscle cells contained desmin but not vimentin, while the connective tissue cells contained vimentin but not desmin.
Concerning the aneurysm walls the majority of the smooth muscle cells in the intima, the media and the adventitia contained vimentin, while only a small portion of these cells contained desmin. However, in the adventitia there were bundles of smooth muscle cells which stained with desmin but not with vimentin.

The morphology of the smooth muscle cells in the aneurysm walls varied greatly. In the media the cells were very thin and elongated, while large cells with a large number of autofluorescent granulae occurred in the intima.

No systematic differences could be demonstrated between the aneurysm walls of patients with and those without AAAs in the family.

Vimentin-containing cells were more common than desmin-containing cells in both normal and aneurysmatic aortic walls. Cells which contained only desmin were located in bundles in the adventitia.

To our knowledge no other study has been published concerning intermediate filament proteins in smooth muscle cells in human atherosclerotic vessels.

DISCUSSION

Familial occurrence of AAAs (I)
In the letter survey there were only two missing cases, and there was no reason to believe that the missing cases were biased. The mean age of the patients in the letter survey was somewhat lower than the mean age of the other patients with AAAs at the time of diagnosis. This may possibly result in a slight overestimation of the frequency of AAAs in the families of patients with AAAs. However, we have reason to suspect that not all the AAAs in the families have been reported and that we instead have underestimated the frequency of AAAs in these families. One reason for these suspicions is that in three cases we discovered by mere chance that patients who had denied that they had any blood relatives with AAAs were in reality of the same families as three other patients with AAAs, who had previously been treated at our clinic. An-
other reason is the high proportion (14/18) of ruptured AAAs among the blood relatives, while only 92/200 of the AAAs treated at our clinic during the same period were leaking or had ruptured. Either the AAAs in the families have a higher tendency to rupture than other AAAs, or the patients have only heard about and reported the dramatic ruptured AAAs in their families.

However, at least 16/87 or 18% of the patients in the letter survey had blood relatives with AAAs. In 9/87 cases (10%) AAAs occurred among their brothers and sisters. The frequency of AAAs among all the brothers and sisters was 9/468 (1.9%), and 7/204 (3.4%) of the dead brothers and sisters had died of ruptured AAAs.

The proportion of the patients, who had brothers and sisters with AAAs, seemed to be higher than expected, but it was difficult to obtain reliable controls with which to compare our results. To estimate how often individuals without AAAs have blood relatives with AAAs, we tried to conduct a letter survey among 89 randomly selected subjects of the same sex and age and from the same communities as the patients. However, only 67 subjects answered the questionnaire. The father of one of these responders had died of a ruptured AAA.

The frequency of AAAs, and especially of ruptured AAAs, among the brothers and sisters of the patients was probably also higher than expected. However, the exact frequency of AAAs in the northern part of Sweden is not known. To estimate this frequency, we tried to obtain information about the number of patients with AAAs, who had been treated at all the clinics of surgery and internal medicine in the area of our university hospital during a ten-year period, but the reported numbers of patients from clinics of the same size varied considerably, and therefore based upon our survey the information obtained was probably not reliable.

In autopsy studies the frequency of AAAs varied between 1% and 6%, but many of the aneurysms in these studies are small, and the majority of them have not been diagnosed clinically and have not ruptured (21-25). Other problems concerning the autopsy studies are, that the autopsy percentage in some studies is low, and that the frequency of AAAs found
at autopsy depends upon the number of AAAs which have been diagnosed clinically and operated on (21, 22).

However, in an autopsy study with a very high autopsy percentage from Malmö in the southern part of Sweden only 24/5,386 or 0.4% of the autopsied patients had clinically diagnosed and/or ruptured thoracic or abdominal aortic aneurysms (21), while 1.9% of the brothers and sisters of the patients in the letter survey had clinically diagnosed and/or ruptured AAAs. The autopsies had been performed during the years 1957-61, when very few patients with AAAs were operated on, while the majority of the AAAs among the brothers and sisters of the patients in our study had been diagnosed in the 1970s. AAAs were slightly more common in the 1970s than in the 1960s, but this can hardly explain the difference.

In the letter survey 7/204 or 3.4% of the dead brothers and sisters had died of ruptured AAAs, while in another autopsy study from Malmö, which comprised the autopsies performed during the years 1957-71, only 42/20,591 or 0.2% of the autopsied patients had died of ruptured atherosclerotic AAAs (30). This difference cannot be explained by the factors which differ between our study and the autopsy study. Ruptured AAAs, which cause the patients death, are probably several times as common among the brothers and sisters of patients with AAAs, as in the general population.

In the literature, we had not found any studies at all concerning how often patients with AAAs have blood relatives with the same disease, or concerning the frequency of AAAs among the brothers and sisters of patients with AAAs. Concerning the pattern of the familial aggregation of AAAs, the majority of the AAAs in our study occurred among the patients' brothers and sisters, while only a few AAAs occurred among their cousins in spite of the fact that there are probably several times as many cousins as brothers and sisters. In the letter survey, nine brothers and sisters but only five cousins had AAAs, and in the other six families with more than one AAA, four brothers and sisters but no cousins had AAAs. The results indicate that there is a predisposition to the development of AAAs among the patients' brothers and sisters, but not among their cousins.
The total number of blood relatives with AAAs in our study was 24, distributed among 22 families. In 20 families there was one blood relative with AAA, and in 2 families there were two blood relatives with AAAs. There was no difference between the patients with and those without AAAs in the family either concerning the proportion between men and women, or the mean age at the time of diagnosis. These results indicate that there is a general predisposition to the development of AAAs among the brothers and sisters of patients with AAAs, rather than that there is a specific group of "familial" AAAs with another etiology than the others.

As already mentioned, a case report concerning familial occurrence of AAAs was presented by Clifton in 1977 (34). In 1984, two studies by Tilson et al have been published concerning familial occurrence of AAAs (64, 65). They were based upon case reports from several different clinics in the United States, and they comprised 50 families with more than one AAA among first degree relatives. In three cases identical twins were affected, and in one of these cases the mother of the twins was also affected. The number of affected individuals in a family was two in 23 cases, three in 21 cases, four in 3 cases, five in 2 cases and six in 1 case. All the affected blood relatives except two were first degree relatives. Individuals from three generations were affected in 3 cases and individuals from two generations in 15 cases. The studies by Tilson et al do not give any information about how common familial occurrence of AAAs is or about the frequency of AAAs among the blood relatives of patients with AAAs, but they do show that there is a predisposition to the development of AAAs in at least some families.

In our letter survey, 2/87 AAA-patients had clinically diagnosed ICAs, and 5/87 other patients had blood relatives with clinically diagnosed ICAs. Thus, it does not seem probable, that the occurrence of all these ICAs is fortuitous. Since ICAs are not usually caused by atherosclerosis (66), there are probably other factors, which predispose to the development of both atherosclerotic and non-atherosclerotic aneurysms in these individuals and in these families. In the literature, we have only found two case reports concerning the occurrence of both AAA and ICA in the same individual (67, 68). Familial occurrence of ICAs is generally accepted (69, 70), and one of the patients in our study had both a brother and a sister with ICAs, and a cousin with an AAA.
Lipids and lipoproteins (II)
In Study II we found, that the patients with AAAs had significantly higher serum concentrations of triglyceride and (VLDL + LDL)-cholesterol, and a significantly lower serum concentration of HDL-cholesterol than healthy controls of the same sex and age. There was no statistically significant difference between the patients with AAAs in the family and those without concerning these serum concentrations. However, if the same pattern of serum concentrations of lipids and lipoproteins is common among the brothers and sisters of the patients and if this pattern predisposes to the development of AAAs, this correlation could explain the high frequency of AAAs among the brothers and sisters.

In the literature, we have only found one study concerning the serum concentrations of lipids and lipoproteins in patients with AAAs. In this study both the serum concentrations of triglyceride and total cholesterol were higher in the patients than in the controls, while the serum concentrations of (VLDL + LDL)-cholesterol and HDL-cholesterol were not reported (41).

In our study a high proportion of the patients (25/51) had occlusive atherosclerotic diseases, and many patients (40/51) were smokers. This is in accordance with the results of other studies (25, 41, 71-73). There were no statistically significant differences between the patients with and those without AAAs in the family concerning the smoking habits or the occurrence of occlusive atherosclerotic diseases.

The large number of patients with occlusive atherosclerotic diseases in Study II could of course explain the deviations from the controls concerning the serum concentrations of lipids and lipoproteins, but when the patients with and without occlusive atherosclerotic diseases were compared concerning the serum concentrations of lipids and lipoproteins, there was no significant difference between them.

Genetic markers (III and IV)
The only studies on AAA-patients, that we have found in the literature concerning the genetic markers studied here are four studies concerning ABO blood groups (43-46) and one study concerning Rh blood groups (47).
Concerning ABO blood groups, a significantly increased frequency of blood group A was found in one of the studies (45), while no statistically significant difference between the patients and the controls was found in the other three studies (43, 44, 46) or in our study. Thus, according to the available information, there is no association between ABO groups and AAAs.

Concerning Rh blood groups, Morris and Bouhoutsos found a significantly increased frequency of Rh-negative AAA-patients (47), while we found a significantly decreased frequency of Rh-negative AAA-patients. Consequently, according to the available information, there is probably no association between Rh blood groups and AAAs.

Concerning the MNSs blood group systems, we found a significantly increased frequency of MN-heterozygotes among the AAA-patients compared with the expected frequency according to the Hardy-Weinberg law. This was more pronounced among the individuals with blood group ss than among the individuals with blood groups SS and Ss. As already mentioned, MN and Ss are two blood group systems, which are closely linked to each other and therefore they are usually inherited as units (63). In spite of this linkage, there was no association between the Ss blood group system and AAA. Concerning the MN blood group system it is suspected that individuals with blood groups MM and MN are more protected than individuals with blood group NN against external factors which affect the serum concentrations of triglyceride and cholesterol (75, 76). However, this cannot explain why, according to our study, MN-individuals have an increased risk of developing AAAs. In our investigation, both the MN blood groups and the serum concentrations of lipids and lipoproteins have been studied in 48 patients. There were no differences concerning the serum concentrations of triglyceride, total cholesterol, (VLDL + LDL)-cholesterol and HDL-cholesterol between the patients with blood groups MM, MN and NN. Consequently, the association between the MN blood group system and AAA in our study does not seem to be mediated by the serum concentrations of lipids and lipoproteins.

Concerning the Kell blood group system, we found a significantly increased frequency of Kell-positive individuals among the patients compared with the controls. Both the Kell blood groups and the serum con-
centrations of lipids and lipoproteins had been determined in 48 pa-
tients, but there was no difference between the six Kell-positive pa-
tients and the 42 Kell-negative patients concerning the serum concen-
trations of the lipids and lipoproteins studied.

In Study IV, we found a significantly increased frequency of individ-
uals with haptoglobin 2-1 type among the patients compared with the
controls, and compared with the expected frequency according to the
Hardy-Weinberg law. There was no difference between the patients with
the different haptoglobin types concerning the serum concentrations of
lipids and lipoproteins (based on 48 patients).

We have found two studies concerning the distribution of haptoglobin
types in patients with myocardial infarctions. In one of them there was
no significant deviation concerning haptoglobin types (77), and in the
other there was a decreased frequency of patients with Hp 2-1 type
compared with the expected frequency according to the Hardy-Weinberg
law (78). Consequently, there is probably not an increased frequency of
the Hp 2-1 type in atherosclerosis per se.

Since no other studies have been reported concerning MN and Kell blood
groups and haptoglobin groups in patients with AAAs, we do not know if
other patients with AAAs have the same pattern as our patients concern-
ing these genetic markers.

Aneurysm walls - morphology (V)
The primary aim of this study was to compare the morphology of the an-
eurysm walls of patients with and without AAAs in the family. Another
aim was to examine the aortic walls for clues to the pathogenesis of
AAAs. Since only a minor portion of the individuals with atherosclero-
sis of the abdominal aorta develop AAAs, it is reasonable to believe
that there are local factors in the aortic wall which predispose to the
development of AAAs. Major strengthening components in the aortic wall
are collagen types I and III (49). Collagen and other components in the
aortic wall are considered to be produced by the smooth muscle cells
(27, 51-53). Therefore it is of interest to study both the occurrence
of collagen types I and III and the smooth muscle cells in patients
with AAAs. The methods we employed in this study were conventional
histology, enzyme histochemistry and immunohistochemistry with antibodies against collagen types I and III and with antibodies against vimentin and desmin in the smooth muscle cells.

With these methods we did not find any differences between the aneurysm walls of patients with and without AAAs in the family. From a morphological point of view, there does not seem to be any specific "familial" AAAs. This is in agreement with the results of our other studies (II-IV), where we could not find any differences between AAA-patients with and without AAAs in the family concerning the serum concentrations of lipids and lipoproteins or concerning the distributions of different genetic markers.

Both collagen types I and III were present in all the aortic specimens. Therefore a deficiency of one of the major collagen types could not explain the development of these AAAs. However, the method employed was not quantitative and does not say anything about the quality of the collagen.

On the basis of vimentin and desmin, we were able to characterize three types of smooth muscle cells in the aortic wall - cells which contain vimentin, cells which contain desmin and cells which contain both vimentin and desmin.

CONCLUSIONS

The results obtained permit the following conclusions:
- Familial occurrence of AAAs is common. In our study 18% of the AAA-patients had blood relatives with clinically diagnosed and/or ruptured AAAs, and of the patients' brothers and sisters 1.9% had clinically diagnosed and/or ruptured AAAs.
- There is usually only one blood relative with AAA, and AAAs are more common among the brothers and sisters than among the cousins of patients with AAAs.
- High serum concentrations of triglyceride and (VLDL + LDL)-cholesterol and a low serum concentration of HDL-cholesterol are common among patients with AAAs whether or not they have AAAs in the family.
- There are high frequencies of individuals with blood group MN, of Kell-positive individuals and of individuals with haptoglobin type 2-1 among patients with AAAS whether or not they have AAAs in the family.

- Both collagen types I and III, and smooth muscle cells containing vimentin, desmin, or vimentin and desmin, are present in the walls of AAAs. There is no difference between the aneurysm walls of patients with and patients without AAAs in the family concerning the morphology.
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