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HABITUAL NOSE-BLEEDING

A clinical study with special reference to occurrence, etiology and treatment

by

Martin Beran

Göteborg 1987
HABITUAL NOSE-BLEEDING

A clinical study with special reference to occurrence, etiology and treatment

AKADEMISK AVHANDLING

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av

MARTIN BERAN
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Avhandlingen baseras på följande delarbeten:


ABSTRACT

HABITUAL NOSE-BLEEDING. A clinical study with special reference to occurrence, etiology and treatment.

MARTIN BERAN, M.D., Departments of Otorhinolaryngology, Anatomy and Medicine II (Coagulation Laboratory) University of Göteborg, Göteborg, Sweden.

Four per cent of the Swedish population are habitual nose-bleeders, i.e. suffer from nose-bleeds several times every year. The causes of these nose-bleeds are largely unknown.

121 subjects with at least four nose-bleeds per year during the preceding two years have been studied. From the answers to a questionnaire, it was found that the bleedings had usually begun during childhood and mostly occurred spontaneously or after minor trauma to the nose. The nose-bleeds were sometimes associated with stress and common colds. Close relatives with frequent nose-bleeds were more often reported among the habitual nose-bleeders than among the controls.

The clinical examination revealed that all habitual nose-bleeders except one had local changes in the nasal mucosa. Abnormal vessels (varicose vessels, telangiomas and a network of small vessels) were found in 102 (84%) habitual nose-bleeders, which was a significantly higher prevalence than in the control group (33%).

Morphologically, varicose vessels and telangiomas in the nasal mucosa were characterised by abnormally large, superficial vessels that bulged into the nasal lumen and were covered with a thin epithelium. The vessel wall consisted merely of a single layer of endothelial cells which in large areas appeared to be degenerated. However, there were also patches of active (proliferating) endothelial cells. The structure of the vessel wall indicates that these pathological vessels were the result of an endothelial growth process and not of dilatation or distension. No specific differences in the structure of the vessel wall could be detected between the varicose vessels and the telangiomas.

Haemostatic disorders were found in 25 (27%) of the tested habitual nose-bleeders. In all cases except one, the defect was in the primary haemostasis. No correlation could be established between the occurrence of haemostatic disorders and abnormal vessels in the nasal mucosa. The bleedings did not seem to be more frequent or of longer duration in the patients with haemostatic disorders than among the other habitual nose-bleeders.

Transection of varicose vessels in the nasal mucosa made the original vessels disappear and reduced the frequency of nose-bleeds. New varicose vessels were quickly formed but in spite of this there was a decrease in bleeding frequency during the two years of follow-up.

It is concluded that recurrent nose-bleeds are most often caused by abnormal vessels in the nasal mucosa. These vessels are probably formed by endothelial proliferation. The propensity to develop abnormal vessels is presumably inherited. Haemostatic disorders were common in the study group but seemed to be of less importance in the explanation of the nose-bleeds than abnormal vessels. Therapy to reduce the frequency of nose-bleeds is available.

Key words: Epistaxis, recurrent, etiology, mucosal changes, vessels, microscopy, endothelial cell turnover, haemostasis, treatment.

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This thesis is based on the following publications, which are referred to in the text by their Roman numerals:


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INTRODUCTION

Nose-bleeding is a common symptom and 60% of a western population have had epistaxis at least once during their lives (Petruson 1974). Most of these people experience single nose-bleeds (occasional nose-bleeders) but four percent of the population have several nose-bleeds every year (habitual nose-bleeders).

Many authors have studied patients with occasional and/or severe bleedings from the nose (Hallberg 1952, Hara 1962, Saunders 1968, Juselius 1974, Petruson 1974, Harrison 1982). On the other hand, studies of patients with repeated, small bleedings are few.

In this investigation, habitual nose-bleeders have been studied with the aim of elucidating the etiology and clinical features.

The blood vessels in the nasal mucosa

The upper parts of the nose are supplied with blood from the internal carotid artery via the anterior and posterior ethmoidal arteries. The external carotid artery supplies the lower and the anterior parts of the nose via the sphenopalatine, the facial and the greater palatine arteries. These vascular systems are connected with anastomoses (Shaheen 1970). Terminal branches of the vessels anastomose in the anterior part of the septum, the Locus Kiesselbach (Cauna 1982).

The vessels in the nasal mucosa are located in the lamina propria (fig 1). The subepithelial layer contains continuous and fenestrated capillaries and arterio-venous anastomoses, embedded in a connective tissue rich in cells and fibrils. In the middle, glandular layer, the capillaries surround the glands. The large blood vessels and sinusoids are located in the deepest, basal layer (Mygind 1979).

The endothelial cells of the subepithelial capillaries may be extremely attenuated. The endothelium is surrounded by scattered pericytes with ability of contraction. The wall of the large vessels (arterioles and venules) and the sinusoids consists of a continuous layer of non-fenestrated endothelial cells and a layer of smooth muscle cells (Cauna and Hinderer 1969).
Fig 1. Light micrograph of normal nasal mucosa from the anterior edge of the lower turbinate.
Epithelium(E); Subepithelial capillaries, $\Phi$ 5-10\(\mu\)m (arrowhead); Glands (arrow);
Sinusoids (asterisks).

Normal haemostasis

The mechanism of haemostasis consists of four components: vessel wall reaction, platelet activation and aggregation, coagulation and fibrinolysis. After injury to a blood vessel, it contracts and platelets adhere to denuded collagen fibres. The adhesion releases platelet factors which increase platelet aggregation, leading to development of a platelet plug, 'primary haemostasis' (Vermylen et al.1983). Between the aggregated platelets, a blood clot is formed by the extrinsic and intrinsic systems of coagulation (Lämmle and Griffin 1985). In the final step of haemostasis, the blood clot is dissolved by fibrinolysis (Erickson et al. 1985).
Etiology of recurrent nose-bleeds

Various diseases and disorders of the nasal mucosa and the haemostasis are known to have recurrent epistaxis as a symptom. The following etiological groups can be identified: defects in the nasal mucosa, tumours in the nose, abnormal vessels in the nasal mucosa and impaired haemostasis.

Defects in the nasal mucosa
Rhinitis anterior sicca and chronic septal ulcer are conditions described to give repeated small bleedings from the nose. In atrophic areas, crusting is frequent and bleedings are considered to occur when these crusts are removed (Saunders 1980). More pronounced atrophy of the septal mucosa may denude the cartilage, resulting in a septal perforation (Manz 1977), from the margin of which recurrent bleedings are common (Johnson 1968, Fairbanks 1980).

Tumours in the nose
Granuloma pyogenicum and haemangioma in the nose are lesions giving recurrent epistaxis as one of the main symptoms (Ash and Old 1950, Wenig et al. 1985). Nose-bleeding, often repeated, is the most common symptom in patients with nasopharyngeal angiofibroma (Witt et al. 1983).

Patients with inverted papilloma or malignant tumours in the nose may have recurrent small nose-bleeds, but in most cases other symptoms such as purulent secretion and obstruction are more prominent (Lawson et al. 1983, Vimpel et al. 1985).

Abnormal vessels in the nasal mucosa
Varicose vessels in the nasal mucosa are often seen in subjects with recurrent nose-bleeds (Shaheen 1979) but they may also be present in subjects without bleedings (Dohlman 1938).

Hereditary haemorrhagic telangiectasia (Mb Osler) has recurrent nose-bleeds together with telangiectatic lesions and inheritance as its main diagnostic criteria (Osler 1901). Morphological studies of the telangiectatic lesions have shown wide vessels with defective vessel walls (Jahnke 1970).
Impaired haemostasis

Frequent epistaxis is a common symptom in patients with 'minor bleeding disorders' (Bachmann 1980). Children with recurrent epistaxis as the sole symptom often have impaired haemostasis (Kiley et al. 1982).

Disorders in the primary haemostasis, such as decreased platelet count or platelet dysfunction, mainly result in bruises and mucosal bleedings (Cronberg 1968). Acetylsalicylic acid blocks the prostaglandin synthesis, which results in an impaired platelet function (Nieuwenhuis and Sixma 1983), and intake of acetylsalicylic acid has been related to nose-bleeds (Petruson 1974).

Nose-bleeds are often seen in blood malignancies, when the platelet count decreases. In Waldenström's macroglobulinemia, the macroglobulin interferes with the platelet function and nose-bleeds are considered an early symptom (MacKenzie and Fudenberg 1972, Wells et al. 1977).

In von Willebrand's disease bleeding from mucous membranes is common and recurrent nose-bleeds occur in more than half of the patients (Silver 1973). The haemostatic disorder is inherited and characterised by a prolonged bleeding time, a defect or decreased level of von Willebrand factor and, in many cases, also a decreased level of factor VIII (Zimmerman and Ruggeri 1983).

Defects in the coagulation are more seldom associated with repeated nose-bleeds. Symptoms in patients with haemophilia A and B have been studied and nose-bleeding was only reported as an occasional symptom (Ramgren 1962). Haemophilia C (factor XI deficiency) often appears without spontaneous bleedings (Edson et al. 1967). Isolated defects of coagulation factor V, VII or X are rare conditions in which nose-bleeds have been described as a symptom (Marder and Shulman 1964, Girolami et al. 1970, Seeler 1972). Treatment with oral anticoagulants reduces the levels of coagulation factors II, VII, IX and X and occasional epistaxis has been reported as a complication of the treatment in about 5% of the patients (Svensson et al. 1985).

Increased fibrinolytic activity in blood and nasal mucosa during nose-bleeding has been demonstrated and suggested to be of importance in the occurrence of repeated nose-bleeds (Petruson 1974). Kwaan and Silverman (1973) reported an increased fibrinolytic activity in telangiectasias in patients with Mb Osler.
Treatment of recurrent nose-bleeds

Nose-bleeds from septal perforations have been shown to decrease after obturation with a septal button (van Dishoeck and Lashley 1975, Kern et al. 1977) or successful operative closure of the perforation (Fairbanks 1980).

Haemangiomas, granulomas or telangiectatic polyps with recurrent nose-bleeds are recommended to be extirpated, together with the underlying perichondrium (Ash and Old 1950, Vaheri 1958, Wenig et al. 1985).

In patients with varicose vessels in the nasal mucosa, cauterisation or electrocoagulation of the vessels is recommended (Shaheen 1979). Transection of the varicose vessel has been shown to reduce the frequency of nose-bleeds (Pinsker and Holdcraft 1971). A limited septal dermoplasty has been performed in patients with troublesome bleedings from a 'fragile septal mucosa' or superficially lying septal vessels with, a long-lasting decrease of the nose-bleeds (Letson and Birck 1973, Beck 1978).

In patients with Mb Osler, septal dermoplasty according to Saunders (1960) has been shown to reduce the frequency of nose-bleeds. (Saunders 1968, McCaffrey et al. 1977, Ulso et al. 1983).

Systemic treatment with estrogen has been reported to reduce the nose-bleeds in patients with Mb Osler but complications from the cardiovascular system may be severe (McCaffrey et al. 1977, Harrison 1982).

Treatment with an antifibrinolytic drug (transexamic acid, Cyklokapron®) has reduced the frequency of bleedings in several patients with Mb Osler (Petruson, personal communication).
DEFINITIONS

*Habitual nose-bleeding:* Bleeding from the nose four times or more yearly during the last two years.

*Mucosal atrophy:* Either of the two mucosal changes defined below.

*Rhinitis anterior sicca:* A clearly visible pale-white and dry area in the anterior part of the septal mucosa and signs of mucosal dysfunction with crusting.

*Septal perforation:* A visible hole in the nasal septum.

*Abnormal vessels:* Any of the four categories of vascular changes defined below, seen on clinical examination after topical decongestion of the nasal mucosa.

*Varicose vessel(s):* A clearly visible vessel of varying thickness and length, usually lying superficially in the septal mucosa. (see Fig. 2, paper II)

*Network of small vessels:* Very thin visible vessels arranged in a network covering a large part of the anterior nasal mucosa.

*Single telangioma:* A small circumscribed, tumorous lesion of vessels with a more or less rough surface, slightly elevated and located mostly on the nasal septum.

*Multiple telangiomas:* More than three telangiomas in the nasal mucosa. (see Fig. 3, paper II)
AIMS OF THE STUDY

The general aim of this investigation was to elucidate the problems connected with habitual nose-bleeders.

The specific aims of the studies were:

- to explore the epidemiology and to establish which diseases or conditions might be associated with recurrent nose-bleeds (I),

- to determine the prevalence of macroscopical changes in the nasal mucosa (II),

- to describe the structure of abnormal blood vessels in the nasal mucosa (III),

- to investigate the prevalence of different bleeding disorders (IV) and

- to evaluate the direct and long-term effects of transection of varicose vessels in the nasal mucosa (V)
STUDY GROUPS

Papers I and II

The study group of these papers comprised 121 subjects with bleeding from the nose four times or more yearly during the preceding two years. The subjects were recruited by means of a medical article in the local newspaper and were asked to contact the clinic. All who replied were sent a questionnaire (see appendix). Those who answered the questionnaire, fulfilled the definition of habitual nose-bleeding and came to an examination at the outpatient clinic were included in the study.

The mean age of the study group was 40 years (range 8-76). Seventy-four (61%) were male and 47 (39%) were female (Fig.2).

![Graph showing distribution of habitual nose-bleeders by age and sex](image-url)
Paper III

Specimens for microscopy of the telangiomas in the nasal mucosa were obtained from 22 habitual nose-bleeders. Biopsy specimens of varicose vessels were taken from 20 patients during transection according to Pinsker and Holdcraft (1971). In 23 habitual nose-bleeders, both with and without abnormal vessels in their nasal mucosa, biopsy specimens of macroscopically normal mucosa were taken from the anterior-inferior edge of the inferior turbinate.

Paper IV

The 121 habitual nose-bleeders in study group (I and II) were invited to participate in a screening examination for bleeding disorders. Ninety-one subjects accepted and were included in the study group of this paper. Fifty-three (58%) were male and 38 (42%) were female. Their mean age was 42 years (range 10-73).

Paper V

Twenty-two habitual nose-bleeders with varicose vessels in the nasal mucosa as the only registered abnormality were operated on with transection of the varicose vessels according to the method described by Pinsker and Holdcraft (1971). Their mean age was 22 years (range 11-52). Thirteen were male and 9 were female. Sixteen of these patients were from the original study group (I and II) and six more entered the study from the outpatient clinic.

CONTROL AND REFERENCE GROUPS

A control group consisting of 121 in-patients were chosen consecutively and matched with the study group for age and sex at the ENT Department, Uddevalla Hospital, Sweden. Patients with all kinds of ENT-diseases were included, except those hospitalised owing to nose-bleeding and those who
were habitual nose-bleeders.  
As reference groups for the blood-pressure measurements, a Bergen population sample (Bøe et al. 1957) and a sample of Swedish schoolchildren (Lindberg and Sigström 1980) were used.

METHODS

Questionnaires (I)

The questionnaire for the habitual nose-bleeders comprised 77 no/yes questions. The patients in the control group answered seven of these questions in a separate questionnaire (see appendix).

Clinical examination (I and II)

The subjects in the study groups and the control group underwent an ENT-examination by the author. Observations from the examination were recorded on a special form. The nasal mucosa was examined before and after decongestion. Photos were taken of changes in the nasal mucosa through a fibre-endoscope (Storz-Hopkins Optik, Ø 4 mm, 1215 A, Storz Lichteinheit 558 B, Olympus OM 1, Kodacolor 400 ASA).

The blood pressure was measured in the seated position after 5 minutes rest. Blood samples were taken for routine tests.

Microscopical examination (III)

The specimens were fixed by immersion in a 2% paraformaldehyde + 2.5% glutaraldehyde mixture in 0.05 M cacodylate buffer. After treatment with osmium tetroxide, they were dehydrated, embedded in Epon and sectioned on Reichert ultramicrotomes. Semithin sections (0.5-1μm) were cut for examination under a Leitz Dialux EB 20 light microscope. Ultrathin sections (~70 nm) were examined in Philips 300 and 400 electron microscopes.
Haemostatic examination (IV)

Screening for haemostatic disorders was performed at the Coagulation Laboratory, Sahlgrenska Hospital, Göteborg, Sweden. The 91 investigated subjects were asked to refrain from taking acetylsalicylic acid for ten days before the examination.

The following screening tests were performed: platelet count, bleeding time according to Ivy, activated partial thromboplastin time (APTT), factor II-VII-X (prothrombin time), fibrinogen, thrombin time, FDP (fibrin(ogen)- degradation products), factor VIII:C and capillary fragility.

Patients with abnormal test results at the screening examination were re-examined and when still abnormal results, extended examination with the aim of diagnosing any haemostatic disorders were performed.

Method of operation and follow-up (V)

The transection of varicose vessels was performed at the outpatient clinic. Topical anaesthesia was used and the varicose vessels were transected horizontally with a pointed scalpel through the mucosa and the peri- chondrium (Fig.3). An anterior gauze tampon soaked in ointment was used to

Fig.3. Position of the horizontal transections in a varicose vessel.
stop the bleeding and was left in place for 48 hours. The extension of the varicose vessels was recorded on special record forms pre- and post-operatively after 1-2 months, 6-9 months, 12-14 months and 24-26 months.

Statistics

The information from the questionnaires and the examination record forms from both the habitual nose-bleeders and the matched controls were computed. When the habitual nose-bleeders were compared with the control group, Pitman's permutation test (Bradley 1968) was applied to the matched groups and the results adjusted according to Mantel 1963 (I and II).

The mean values of the blood pressures of the different age-groups in the population samples used as reference groups (Bøe et al. 1957, Lindberg and Sigström 1980) were connected by lines. The blood pressures of the habitual nose-bleeders were plotted and compared with these mean value lines. The Sign test was used to test whether there was any difference in blood pressure between the population samples and the habitual nose-bleeders (I).

RESULTS AND CONCLUSIONS

Occurrence of nose-bleeds (I)

The nose-bleeds started during childhood in more than half of the habitual nose-bleeders and most of them stated that they had bled repeatedly for the last ten years. More than two-thirds of the subjects had bled at least once a month during the preceding two years. The bleedings were usually of short duration and ceased within ten minutes. Seven out of ten had consulted a doctor due to nose-bleeding and one tenth of these had been hospitalised.

Most bleedings started spontaneously but minor trauma to the nose, like picking or blowing the nose, also initiated nose-bleeds. More than half of the nose-bleeders answered that the bleedings were connected with stress and/or tiredness and common colds.
Conclusions

Most of the habitual nose-bleeders had suffered from recurrent bleeding for many years. The bleedings mostly started without any obvious reason and at other times in connection with minor trauma to the nose, a common cold or a stress situation.

Diseases, routine blood tests and blood pressure in the study group (I)

More than seven out of ten bleeders were healthy, without any disease known to them. Some cardiovascular disorders were reported among the bleeders over 40 years of age as might be expected in this age-group. Anaemia was observed in fifteen habitual nose-bleeders. Two of them, who said that they bled from the nose every day, had a haemoglobin concentration below 100 g/l. An increased ESR were found in ten of the nose-bleeders. Only one, a pregnant woman, had an ESR above 50 mm/h. Most of the other results of the routine blood tests were within the reference values of the hospital. No significant difference was found when the blood pressures of the habitual nose-bleeders were compared with the mean blood pressures of the reference groups.

Conclusions

Most of the habitual bleeders had no systemic disease of which the nose-bleeds could be regarded as a symptom. In some nose-bleeders, the loss of blood resulted in anaemia.

Mucosal atrophy and abnormal vessels in the nasal mucosa (II)

All habitual nose-bleeders except one had nasal mucosal changes. One third had more than one registered change. The prevalence of both mucosal atrophy and abnormal vessels was significantly higher among the habitual nose-
bleeders than among the controls. Mucosal atrophy without concomitant presence of abnormal vessels was, however, equally common in both groups. Abnormal vessels (varicose vessels, telangioma or a network of small vessels) were found in 102 (84%) nose-bleeders. Varicose vessels were the most frequent abnormality but were also seen in the control group. Telangioma and a network of small vessels were only seen among the habitual nose-bleeders.

Conclusion

Abnormal vessels, observed in more than eight out of ten habitual nose-bleeders, probably explain most of the recurrent bleedings.

Morphology of varicose vessels, telangiomas and macroscopically normal mucosa (III)

The abnormal vessels bulged into the nasal lumen and were covered with sparse connective tissue and a rather thin epithelium. The varicose vessels were isolated very wide vascular channels and the telangioma consisted of multiple closely apposed wide vessels. The diameter of these vessels were up to one hundred times larger than normal subepithelial capillaries. However, no specific morphological feature of the vessel wall structure that distinguished the two lesions could be discerned.

The vessel wall lacked smooth muscle cells and pericytes forming an organised media as would be expected in normal vessels of comparable size. The endothelium consisted of a single layer of mostly thin and seemingly degenerating cells that at some points even failed to form a continuous tunic. At other spots, organelle-rich endothelial cells could be seen as well as endothelial cells of 'normal' appearance. Particularly in telangiomas, multiple-layered periendothelial basal lamina was observed, indicating an increased vascular wall turnover.

The biopsies from the inferior turbinate had an intact mucosal lining with apparently normal mucosal vessels.
Conclusions

The abnormal vessels were wide, with a superficial position in the nasal mucosa. They were thin-walled, with mostly degenerating endothelium, and lacked elements for contraction. It is obvious that they might easily rupture and bleed. The presence of scattered, active, organelle-rich endothelial cells suggests that these vessels are formed by cell multiplication, not by distension or dilatation of a normal vessel.

Heredit (I and II)

The habitual nose-bleeders stated that their close relatives (parents, brothers and sisters) had recurrent nose-bleeds significantly more often than did the controls.

Close relatives of the bleeders with varicose vessels in the nasal mucosa as the sole local change had recurrent nose-bleeds significantly more often than relatives of the patients from the control group without varicose vessels.

Conclusion

The propensity to have recurrent nose-bleeds is presumably inherited.

Haemostatic disorders (IV)

Eleven of the 91 tested nose-bleeders had increased capillary fragility as the only abnormality. Fourteen (17%) were found to have a haemostatic defect, all except one in the primary haemostasis. Four of these had a mild form of von Willebrand's disease.

No connection could be established between the haemostatic disorders and the presence of abnormal vessels in the nasal mucosa. Only a tendency to increased bleeding frequency and longer duration of the bleedings could be observed in the nose-bleeders with haemostatic disorders.
Conclusions

Every fourth habitual nose-bleeder had a haemostatic disorder. The occurrence of abnormal vessels in the nasal mucosa could not be correlated to the haemostatic disorders. Although plausible, it could not be proven that impaired haemostasis gave longer or more frequent bleedings.

Treatment of varicose vessels by transection (V)

After transection, the decrease in frequency of nose-bleeds was significant during both years of follow-up. Slight mucosal atrophy at the transection site was observed on one-third of the operated sides. The original varicose vessel could not be seen at the first postoperative control. However, new varicose vessels were formed at new sites and after two years almost all patients had new varicose vessels.

Conclusions

The transection made the original varicose vessels disappear and markedly reduced the frequency of nose-bleeds. In spite of the rapid formation of new vessels, the frequency of nose-bleeds remained low during the two years of follow-up.

GENERAL DISCUSSION

Many people have experienced nose-bleeding. Most of them have had single nose-bleeds but four per cent suffer from repeated bleedings (Petruson 1974). Several studies have been performed on patients with occasional or severe bleedings from the nose but little attention has been paid to nose-bleeders suffering from recurrent small bleedings. It was therefore decided to study subjects with habitual nose-bleeding and invite them to participate in this investigation by means of an article in the local newspaper.
From the findings in this investigation the typical history of a habitual nose-bleeder can be summarised as follows:

A middle-aged, subjectively healthy, person of either sex who has experienced repeated nose-bleeds since childhood and for the last two years has had bleedings from the nose at least once a month. The bleedings are generally of short duration. They often occur spontaneously and sometimes in connection with a stress situation. Blowing or picking the nose may easily result in a bleeding. Many close relatives also suffer from repeated nose-bleeds. The patient has not observed any other bleeding tendency.

Atrophy of the nasal mucosa has been related to recurrent nose-bleeds (Manz 1977, Saunders 1980, Fairbanks 1980). In this study, mucosal atrophy, as the only observed defect in the nasal mucosa, was observed in 15 per cent of the habitual nose-bleeders and was as common in the control group. The bleedings in the nose-bleeders may possibly be explained by a more pronounced mucosal atrophy but the possibility of an undiscovered abnormal vessel in the nasal mucosa cannot be excluded.

Coincident presence of mucosal atrophy and abnormal vessels in the nasal mucosa was more common in the habitual nose-bleeders than in the controls. It is known that mucosal atrophy develops over a long period of time when the nasal mucosa is exposed to irritants (Hussarek 1968) and it therefore seems probable that the mucosal atrophy in the nose-bleeders with abnormal vessels develops as a consequence of repeated trauma to the nose e.g. from the efforts to stop the bleedings.

Varicose vessels in the nasal mucosa were the most commonly recorded change in the habitual nose-bleeders. These vessels have earlier been described in connection with repeated nose-bleeds (Pinsker and Holdcraft 1971, Shaheen 1979) but may also occur in the nasal mucosa without nose-bleeding (Dohlman 1938). One-third of our control patients had varicose vessels in the nasal mucosa without habitual nose-bleeding. After transection, the new varicose vessels that were formed had a low tendency to bleed.

The tendency of some varicose vessels to bleed might depend on a larger
diameter, thinner walls, greater extension or more superficial position in the nasal mucosa.

In patients with Mb Osler, repeated nose-bleeds are known to come from the telangiectasias in the nasal mucosa (Saunders 1980, Harrison 1982). Seven of the habitual nose-bleeders had Mb Osler and more than one-fourth of the nose-bleeders had single telangiomas in the nasal mucosa, while no such changes were present in the controls. This shows that even the presence of single telangiomas is correlated to repeated nose-bleeds.

The morphological examination of the varicose vessels and telangiomas showed that the diameter of the vessels was up to one hundred times larger than normal subepithelial capillaries. The vessels had a superficial position in the nasal mucosa, being covered by only a sparse layer of connective tissue and a thin epithelium. The vessel wall was delicate, with most areas lined by very or extremely thin endothelial cells. Periendothelial cells with contraction ability, i.e. pericytes and smooth muscle cells, were almost completely absent. It seems reasonable to assume that a vessel with such a structure, situated in a mucosa often subjected to trauma, may rupture easily and cause a nose-bleed. The distending force in the vascular wall is proportional to the diameter times the pressure (Laplace's law), which means that in these huge vessels even moderate pressure will give a considerable distending force on the weak vessel wall.

Once a bleeding from these vessels has started, the clotting mechanisms alone will be responsible for the control of haemorrhage since local vessel contraction cannot be elicited in the absence of smooth muscle cells in the vessel wall. Furthermore, the ability to form a platelet plug is probably also impaired as the platelets will meet no or very little collagen, which is necessary for platelet adhesion (Santoro and Cunningham 1981), due to the sparse layer of connective tissue between the vessel wall and the epithelium.

Disorders of especially the primary haemostasis are known to cause nose-bleeds (Cronberg 1968, Silver 1973, Bachmann 1980, Kiley et al 1982). The disorders in the habitual nose-bleeders were all in the primary haemostasis
except one, and the prevalence of such disorders was more than a hundred times higher than estimated in a normal population (Bachmann 1980). One would expect that habitual nose-bleeders with haemostatic disorders would have more frequent and severe bleedings than the other nose-bleeders but such a connection could not be proven. Nor were there any connections between haemostatic disorders and the presence of abnormal vessels in the nasal mucosa. It is therefore probable that the reduced capacity of local haemostasis as indicated above plays a more important role in recurrent nose-bleeds than minor general haemostatic disorders.

However, since so many haemostatic disorders were found, some of them of clinical importance, it seems reasonable to offer habitual nose-bleeders a limited investigation of the haemostasis, with determination of the bleeding time according to Ivy, platelet count, APTT and prothrombin time.

Telangiomas collected from patients with Mb Osler had the same morphology as the lesions from patients with single telangiomas. Although the telangioma and varicose vessel had a different gross organisation in the nasal mucosa, the structure of the vessel wall was similar. It was also found that 13 habitual nose-bleeders had telangiomas in the nasal mucosa together with varicose vessels. Close relatives to the habitual nose-bleeders with abnormal vessels in the nasal mucosa often had repeated nose-bleeds but whether these bleedings were caused by abnormal vessels in the nose is unknown. These observations suggest that the familial tendency to have repeated nose-bleeds might be coupled to a hereditary disposition to form abnormal vessels.

As previously mentioned, large areas of the endothelium in telangiomas and varicose vessels appeared to be degenerating, whereas regional accumulations of 'active' endothelial cells were seen. These observations indicate that the vessels obtain their dimensions by proliferation of endothelial cells and not by passive dilatation. The rapid formation of new varicose vessels after transection also indicates that the vessels are created by an active process.

An interesting biological question is which angiogenetic factor(s) governs the formation of abnormal vessels in the nasal mucosa. Angiogenetic substances, which have been isolated from tumours and normal tissues, can give a signal
to endothelial cells to generate new capillaries. However, in normal tissue, anti-angiogenetic substances control and regulate the formation of new capillary vessels. The turnover of endothelial cells is in most tissues measured in years. It has been suggested that alterations in the equilibrium between angiogenetic and anti-angiogenetic factors may induce growth or regression of microvessels (Folkman 1986, Schor and Schor 1983).

It is well known that angiogenesis is induced by a proceeding inflammation and several angiogenetic substances have been demonstrated in inflammatory cells (Schor and Schor 1983). Dicumylperoxide produced an inflammatory reaction in the nasal mucosa of rabbits and superficial vessels were quickly formed as reported by Hansson and Petruson (1986). Furthermore, workers exposed to dicumylperoxide more often had visible vessels in the nasal mucosa than subjects working at a hospital (Petruson and Järvholm 1983).

However, the habitual nose-bleeders in this study were not exposed to any known specific factor in the environment causing inflammation. Nor had they had more common colds or were more allergic than could be expected. It therefore seems probable that constitutional factors govern the formation of abnormal vessels in the habitual nose-bleeders.

Treatment of patients with habitual nose-bleeding includes giving them information on the etiology and how to handle their nose in order to avoid bleedings.

In the habitual nose-bleeders with mucosal atrophy and crusting, cleaning the nose with a salt solution and moistening the atrophic area with oil or ointment was recommended and seemed to be of value.

Bleedings from the margin of a septal perforation may diminish after obturation of the perforation with a septal button (van Dishoeck and Lashley 1975, Kern et al. 1977) or disappear after successful operative closure (Fairbanks 1980).

Varicose vessels of small extension can be cauterised, e.g. with chromic acid. When the varicose vessels are more extended, transection of the vessels is a simple and efficient method of reducing the frequency of nose-bleeds. In some patients, the result of transection may be insufficient and a circumscribed dermoplasty may be considered (Letson and Birck 1973, Beck 1978).
Single lesions, such as telangiomas or haemangiomas, in the nasal mucosa are suitable for surgical extirpation, including the underlying perichondrium (Wenig et al. 1985), as were done in the habitual nose-bleeders with single telangiomas in this study.

There is an increased fibrinolytic activity in telangiomas from patients with Mb Osler (Kwaan and Silverman 1973) and systemic treatment with an antifibrinolytic drug (tranexamic acid, Cyklokapron®) has been found to reduce the frequency of nose-bleeds (Petruson 1986, personal communication).

Septal dermoplasty is a good method of reducing the bleedings in patients with Mb Osler (Saunders 1968, McCaffrey et al. 1977, Ulsø et al. 1983) and was performed in two of the habitual nose-bleeders with this disease.

Systemic treatment with estrogen decreases the bleedings from the nose but is associated with various complications and should therefore be used with discretion and only when other treatments have failed (McCaffrey et al. 1977, Harrison 1982).

Visible vessels in patients with recurrent nose-bleeds and telangiectasias in patients with Mb Osler have been treated with the Argon-Laser technique (Lenz and Eichler 1984). However, it is too early to evaluate this therapy as the effects on the nasal mucosa, the septal cartilage and formation of new vessels are largely unknown.
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APPENDIX

The questions with figures in bold print were included in the shorter questionnaire for control subjects.

QUESTIONNAIRE FOR SUBJECTS WITH RECURRENT NOSE-BLEEDS

Name................................................................. Address.................................................................

Telephone......................................................... Date of birth.......................................................

Date, when answering the questions..........................

1. AGE. How old are you? ........................................... years of age

2. SEX. ............................................................... male ☐ female ☐

NUMBER OF NOSE-BLEEDS

3. How long have you had nose-bleeds several times every year? ☐ last 2 years
   ☐ last 10 years ☐ more than 10 years

4. Have you had recurrent nose-bleeds every year ☐ since childhood?
   ☐ since teenage? ☐ only as an adult?

5. How many nose-bleeds have you had during the last two years? ☐ less than once/year
   ☐ 1-3 times/year ☐ 4-6 times/year
   ☐ 6-12 times/year ☐ more than 12 times/year

6. Do you generally have nose-bleeds at least ☐ once a month
   ☐ once a week ☐ once a day

NOSE-BLEEDS LAST WEEK

7. Have you had a nose-bleed during the last 7 days? ☐ no ☐ yes

8. Have you had a common cold during the last 7 days? ☐ no ☐ yes

9. Have you taken any drug for pains containing acetylsalicylic acid (e.g. Albyl, Aspirin, Bamyl, Doleron, Dispril, Magnecyl, Spalt, Treo) during the last 7 days? ☐ no ☐ yes
DURATION OF THE NOSE-BLEEDS

10. How long do you generally bleed from the nose at each bleeding episode?
   - less than 5 min.
   - 5-10 min.
   - 10-30 min.
   - 30-60 min.
   - more than 1 hour

11. Once a bleeding has started, during what time do new bleedings occur after the first bleeding has ceased?
   - 1 day
   - 2-4 days
   - 5-7 days
   - more than 7 days

12. How long do you generally have to stay at home or rest at work when you have nose-bleeds?
   - need no rest
   - less than 1 hour
   - 1-4 hours
   - 5-8 hours

13. Do you sometimes have to stay at home for days due to nose-bleeds?
   - no
   - yes, 1 day
   - yes, 3-4 days
   - yes, 5-7 days
   - yes, more than 7 days

14. How many days per year must you stay at home due to nose-bleeds?
   ......... days

TREATMENT FOR NOSE-BLEEDS

15. Have you consulted a doctor due to nose-bleeding?
   - no
   - yes, ........ times

16. How many times have you consulted a doctor due to nose-bleeding during the last two years?
   ......... times

17. Have you ever been admitted to hospital due to nose-bleeding?
   - no
   - yes, ........ times

18. How many times have you been admitted to hospital during the last two years?
   ......... times

REASONS FOR THE NOSE-BLEEDS

19. Do you often bleed from the nose in connection with colds?
   - no
   - yes

20. Do you often bleed from the nose when you have taken medicine containing acetylsalicylic acid? (see question 9)
   - have not noticed any connection
   - have noticed a connection

21. Do you often bleed from the nose in connection with stress and/or tiredness?
   - no
   - yes
22. Do you often bleed from the nose in connection with physical strain, e.g. heavy lifts or sports? □ no □ yes
23. Do you often bleed from the nose during menstruation? □ no □ yes
24. Have you noticed any other connection with the nose-bleeds? What connection?..........................
25. Do you often bleed after picking your nose? □ no □ yes
26. Do you often bleed after blowing your nose? □ no □ yes
27. Do you often bleed without any obvious reason? □ no □ yes
28. Do you often bleed at a special time during the day? □ no □ yes
29. If so, at what time of the day? Between...........and...........o'clock.

HEREDITY

30. Does or did either of your parents often have nose-bleeds? □ no □ yes
    Whom?...........................................................................
31. Does any of your children often have nose-bleeds? □ no □ yes
    Whom?...........................................................................
32. Does any of your brothers or sisters often have nose-bleeds? □ no □ yes
    Whom?...........................................................................
33. Does any of your other close relatives often have nose-bleeds? □ no □ yes
    Whom?...........................................................................

BLEEDING TENDENCY

34. Are there any inherited blood disease among your relatives? □ no □ yes
    What disease?......................... In whom?.........................
35. Do you think that you bruise abnormally easily? □ no
    □ yes-on the arms
    □ yes-on the body
36. Do you think that you bleed longer than normal from a skin cut? □ no □ yes
37. Do you think that you bleed more or longer than normal after a tooth extraction? □ no □ yes
DISEASES

Have you been or are you being treated for:

   yes, not treated
   no
   yes, formerly treated
   yes, still on treatment

39. Diabetes? ...........................................................
   yes, not visible on X-ray
   yes, visible on X-ray
   yes, operated on

40. Liver disease? Which? ............................................
   yes, not operated on
   yes, operated on

41. Kidney disease? Which? ...........................................

42. Heart disease? Which? ...........................................

43. Disease of the blood vessels? Which? ......................

44. Joint disease? Which? ...........................................

45. Have you had a peptic ulcer?
   When? ..............................................................

46. Have you had gastric bleeding?
   When? ..............................................................

47. Has any doctor told you that you are suffering from hypertension?

48. Do you often suffer from headache?

49. Do you often suffer from rheumatism?

MEDICINE

50. Are you being treated continuously with any medicine?
   no
   yes

51. How often do you take medicine for aches and pains?
   (see question 9)
   never, or occasionally
   at least once a month
   at least once a week
   at least once a day
   1-3
   4-5
   more than 6

52. When you take medicine for aches and pains, how many tablets do you usually take daily?
   no
   yes

53. Do you generally take medicine for aches and pains when having a common cold?
   no
   yes

54. Do you generally take medicine for aches and pains during menstruation?
   no
   yes
DISEASES AND OPERATIONS ON THE NOSE

55. Do you have any trouble with nasal blockage?
   - no
   - yes, sometimes
   - yes, constantly

56. On which side of the nose do you have nasal blockage?
   - the right side
   - the left side
   - both sides

57. Are you often troubled by mucous secretion from the nose?
   - no
   - yes

58. Do you often have to remove crusts from your nose?
   - no
   - yes

59. How often do you have colds?
   - less than once a year
   - once a year
   - 2-4/year
   - more than 4/year

60. Have you ever had sinusitis?
   - no
   - yes, once
   - yes, several times

61. Have you ever been irrigated for sinusitis?
   - no
   - yes, once
   - yes, several times

62. Do you usually bleed for a long time after the irrigation?
   - no
   - yes

63. Have you had any operations on your sinuses?
   - no
   - yes

64. Do you have or have you had hay fever?
   - no
   - yes, several years ago
   - yes, last couple of years

65. Have you had nasal polyps?
   - no
   - yes, several years ago
   - yes, last couple of years

66. Have you been operated on for nasal polyps?
   - no
   - yes, several years ago
   - yes, last couple of years

67. Have you had any other operations on your nose?
   - no
   - yes

68. If so, when?..........................and for what?..........................
WORK ENVIRONMENT

69. Are there gases, dirt or dust at your place of work that irritate your nose?  □ no  □ yes

70. If so, what kind of substances? .................................................................

71. Do you usually get nose-bleeds when something irritates your nose?  □ no  □ yes

SMOKING HABITS

72. Have you smoked regularly during any period of your life?  □ no  □ yes

73. Do you smoke at present?  □ no  □ yes

74. When you smoke, do you blow the smoke out through your nose?  □ no  □ yes

75. Have you noticed any connection between smoking and your nose-bleeds?  □ no  □ yes

MISCELLANEOUS

76. Have you noticed that the nose-bleeds occur in special situations? If so, what situation? .................................................................

77. Does the bleeding generally come from the same side?  □ no  □ yes, the right side  □ yes, the left side
På grund av upphovsrättsliga skäl kan vissa ingående delarbeten ej publiceras här. För en fullständig lista av ingående delarbeten, se avhandlingens början.

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