EPISTAXIS

AN INVESTIGATION INTO NASAL HÆMORRHAGE

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In the course of an investigation into the cause of nasal hæmorrhage, Dohlman (1938) drew attention to interesting microscopic findings in biopsy specimens taken from that portion of the nasal epithelium known as Little's area. In a large number of investigated cases Dohlman found a relative absence of inflammation, a poor attempt at healing and the presence of deep venous plexus thrombosis. From these findings he concluded, that in the ætiology of nasal hæmorrhage, in addition to the more obvious pathological conditions, there were certain " endogenous " factors to be taken into consideration, which contribute to the initiation and recurrence of epistaxis. Dohlman, however, made no suggestions as to what these factors might be.

In an attempt to identify what additional factors may be responsible for epistaxis, a series of 100 consecutive cases were examined as they presented at the Out-patient Department of the Ear, Nose and Throat Unit at the Glasgow Royal Infirmary. A careful case history was taken and in each case the following investigations were carried out : ascorbic acid levels, prothrombin time, serum calcium, coagulation time and bleeding time. Note was taken of the site of bleeding and it was also ascertained whether it was the first attack of hæmorrhage or a recurrence. No distinction was made between very severe cases of nasal hæmorrhage which necessitated admission and those who had only mild attacks of epistaxis. Only seven of the patients, all of whom suffered from hypertension, had to be admitted, and these were transferred, after the epistaxis had been dealt with, to medical wards.

Likewise, no case presenting an apparent pathological cause for the hæmorrhage was omitted, as it was felt that one or other of the " endogenous " factors under investigation, or combination of them, superimposed on the predominant ætiological factor might increase the number of attacks of bleeding or add to their severity.

Methods

The estimation of the ascorbic acid content was carried out according to the method described by Harris and Ray (1935). The essence of this

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consists in the estimation of the urinary ascorbic acid before and after the administration of 300 mg. ascorbic acid on two consecutive days.

Figures in health vary widely, but it is assumed that scurvy can only be excluded when the second sample of urine contains at least double the concentration of the first. In order to have some measure of the deficient ascorbic acid concentration in a particular patient, a varying number of " minus " signs was introduced in the chart.

For the estimation of the prothrombin time, the method described by Quick, Stanley-Brown and Bancroft (1935) was used. The principle of this method is, that all factors required for clotting except prothrombin are supplied in excess so that prothrombin is the only limiting factor. The series of reactions is produced by the addition of calcium and thrombokinase to an oxalate sample of plasma and the time from its addition until appearance of the clot is the " prothrombin time ". The thrombokinase extract used was an ox lung preparation. A normal control patient was used in each estimation for comparison. Once the efficiency of the thrombokinase deteriorated to the extent that a normal control specimen clotted in more than 20 seconds, it was discarded. Thereby a blood specimen under observation, which gave prothrombin time of less than 25 seconds, was regarded as normal.

For the estimation of serum calcium, the method described by Kramer and Tisdall (1921) was used and values of 9-11·5 mg. per cent. were taken to be normal.

For the estimation of the clotting time, the same procedure as used for the determination of prothrombin time was employed, but the thrombokinase was displaced by an equal amount of 0·9 per cent. NaCl. Values up to 150 seconds were taken as normal.

The bleeding time was estimated by applying filter paper to the blood issuing from a needle prick. Values up to 4 minutes were taken to be normal.

A hæmorrhage was termed anterior or " A " in the chart, when the bleeding occurred anterior to a vertical line arbitrarily drawn through the middle of the inferior turbinate; and posterior or " P " in the chart, when the bleeding took place behind the vertical line.

Discussion

Amongst the 100 patients, who presented themselves at the out-patients department, there were 59 males, ranging from 5 to 73 years of age, and 41 females, ranging in age from 13 to 82 years. In 65 patients, a previous hæmorrhage had occurred, and in the remaining 35 it was the first episode.

There were 20 patients, in whom both the ascorbic acid level and the prothrombin time were normal, 14 of whom were males and 6 females. Thirty patients showed normal and 70 subnormal ascorbic acid levels.

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Epistaxis

Case	Sex	Age	Ascorbic acid	Prothrombin time in seconds	Coagulation time	Area	Comment
1	M	20	— —	32	N	A	Chronic sinusitis
2	F	18	— — —	31	P	A	Atrophic rhinitis
3	M	48	—	27	N	P	Hypertension
4	F	46	— —	19	N	A	Acute coryza
5	F	70	—	26[3]	N	P	Ulceration of septum
6	M	25	+	20	N	A	Post-operative (S.M.R.)
7	M	17	— —	28	N	A	Chronic sinusitis
8	M	71	+	29	N	P	Hypertension
9	M	42	+	20	N	A	Pernicious anæmia
10	M	16	+	25	N	A	Ulceration of septum due to picking
11	F	62	—	33	P	P	Hypertension
12	F	45	— —	29	N	A	Rheumatic heart disease
13	M	24	+	20	N	A	Nasal polyp
14	M	66	— —	32	N	A	Septal deflection
15	M	45	— —	24	N	A	Perforation of septum due to chromic acid
16	M	51	—	24	N	P	Polyposis
17	M	13	+	18	N	A	Post-nephritis
18	M	27	—	26	N	A	Post-antrostomy
19	M	56	—	28	P	P	Hypertension
20	F	44	—	29	N	A	Hypertension
21	M	45	— — —	26	N	P	Chronic nephritis
22	M	38	—	22	N	A	Septal deflection
23	M	21	— —	28	N	A	Anæmia

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Case	Sex	Age	Ascorbic acid	Prothrombin time in seconds	Coagulation time	Area	Comment
24	M	62	+	22	N	P	Chronic sinusitis
25	M	46	— —	21	N	P	Hypertension
26	M	25	— —	23	N	A	Perforated septum
27	M	29	—	24	N	A	
28	F	60	— —	20	N	P	Arterio-sclerosis
29	M	48	—	25	N	A	
30	F	36	+	23	N	A	Septal deflection
31	M	28	— — —	29	N	A	
32	F	63	—	22	N	P	Hypertension
33	M	34	—	20	N	A	Crusting
34	M	58	— — —	29	N	A	Chronic sinusitis
35	M	29	+	22	N	A	
36	M	25	— —	24	N	A	Anæmia
37	F	29	— —	20	N	A	Post-radical antrostomy
38	M	67	+	21	N	P	Hypertension
39	M	21	— —	24	N	A	Acute coryza
40	F	28	— — —	20	N	A	Nasal polypus
41	M	13	— —	18	N	A	Deflected septum
42	M	16	+	22	N	A	Ulcer of septum due to picking
43	F	23	—	20	N	A	Tuberculosis
44	F	49	— —	29	N	P	Chronic nephritis
45	F	52	—	33	N	P	Hypertension
46	M	46	+	29	N	A	
47	F	60	— —	20	N	P	Ulceration of septum
48	M	18	—	18	N	A	Lupus erythematosus

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Epistaxis

Case	Sex	Age	Ascorbic acid	Prothrombin time in seconds	Coagulation time	Area	Comment
49	M	17	— —	28	N	A	Psoriasis
50	F	72	+	33	N	P	
51	M	13	—	34	N	A	Rheumatism
52	M	73	— — —	26	N	P	Hypertension
53	F	64	+	21	N	P	Hypertension
54	M	51	— — —	21	P	A	Trauma to nose
55	F	77	— —	33	N	P	Hypertension
56	F	76	—	19	P	P	Hypertension
57	F	22	— — —	22	N	A	Chronic sinusitis
58	F	9	— —	18	N	A	Adenoids enlarged
59	F	29	+	32	N	A	Congenital syphilis
60	M	15	+	20	N	A	Trauma to nose
61	M	57	—	29	N	A	Septal deflection
62	M	58	—	18	N	P	Hypertension
63	F	14	+	22	N	A	Foreign body in nose
64	F	13	— — —	18	N	A	Picking of nose
65	M	44	—	23	N	A	Ulceration of septum
66	F	53	+	28	N	P	Polypi
67	M	60	—	28	N	P	
68	F	56	+	20	N	A	Crusting
69	M	57	+	34	N	A	Ulceration of septum
70	M	50	—	20	N	P	Hypertension
71	F	14	— —	32	N	A	Deviated septum
72	M	64	—	25	N	A	Hypertension
73	M	43	— —	19	N	A	

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Case	Sex	Age	Ascorbic acid	Prothrombin time in seconds	Coagulation time	Area	Comment
74	M	18	— —	19	N	A	Perforated septum
75	F	56	+	36	N	P	Hypertension
76	F	64	+	33	N	P	Hypertension
77	F	72	—	24	N	P	Hypertension
78	M	9	— —	18	N	A	Rheumatic fever
79	M	12	+	22	N	A	Septal deflection
80	M	29	— —	33	N	A	
81	M	46	—	18	N	A	Chronic sinusitis
82	F	49	+	36	N	P	Acute coryza
83	M	5	—	19	N	A	Endocarditis
84	F	17	— —	20	N	A	Septal deflection
85	F	82	— — —	32	N	P	Hemiplegia, hypertension
86	F	16	+	18	N	N	Chronic sinusitis
87	M	23	+	24	N	A	Ulcer of septum
88	F	29	—	25	N	A	Tuberculosis
89	F	64	— —	30	P	P	Hypertension
90	M	72	—	23	N	P	Hypertension
91	F	18	— —	18	N	A	
92	M	14	— —	29	N	A	
93	M	10	+	18	N	A	Septal deflection
94	M	12	— —	16	N	A	Traumatic
95	F	73	—	33	N	P	Hypertension
96	M	64	+	18	N	P	Hypertension
97	M	19	— — —	20	N	A	Chromic acid ulcer
98	F	42	+	24	N	A	

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Epistaxis

Case	Sex	Age	Ascorbic acid	Prothrombin time in seconds	Coagulation time	Area	Comment
99	F	19	—	26	N	A	Post-radical antrostomy
100	F	2	+	19	N	A	Chronic sinusitis

+ Indicates that second sample of urine contains at least double the concentration of the first.

— Indicates that the second sample of urine contains 50 per cent. or more, but not double, the first specimen.

— — Indicates that the second sample of urine contains 25 per cent. or more, but not 50 per cent., of first.

— — — Indicates that the second sample of urine contains less than 25 per cent. increase on first.

" N " Indicates normal ; " P " indicates prolonged.

" A " Indicates anterior hæmorrhage ; " P " indicates posterior hæmorrhage.

The columns for serum calcium and bleeding time were omitted from the chart, as they showed normal results in all cases.

Amongst those showing normal ascorbic acid levels there were 17 males and 13 females; in those with subnormal levels there were 42 males and 28 females. Sixty patients had a normal prothrombin time, 39 of whom were males and 21 females. Thirty-one patients in addition to having subnormal ascorbic acid levels had also a prolonged prothrombin time. On the other hand 9 patients with normal ascorbic acid readings showed a subnormal prothrombin activity. Thus a total of 40 patients exhibited a subnormal prothrombin level. There were 39 patients, who showed subnormal ascorbic acid levels with normal prothrombin time.

In order to determine whether the deficiencies of ascorbic acid and prothrombin are more prevalent in special age groups, the patients were divided arbitrarily into the following three categories : up to 15 years ; 15 to 40 years of age ; above 40 years of age. The 70 patients with deficient ascorbic acid levels were thus divided into the three mentioned groups according to their age. There were 9 in the first group, 25 in the second group and 36 in the third group. The same sub-division was made amongst the 40 patients with prothrombopenia. The first group comprised 3, the second 12 and the third 25. It is seen that the proportion of both Vitamin C and Vitamin K deficient patients is highest in the old age groups and lowest in the children group.

The serum calcium content was normal in all patients. The coagulation time was prolonged in 7 cases. In 4 of these the ascorbic acid and prothrombin levels were subnormal, in one patient there was a prolongation of the prothrombin time with normal ascorbic acid level and in the remaining 2 the prothrombin time was within normal limits, but in one of the two cases there was a gross deficiency of Vitamin C and in

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the other there was a minor degree of deficiency. No other cause could be found to explain the prolonged clotting time.

The bleeding time was normal in all cases. There were 67 " anterior " and 33 " posterior " hæmorrhages. The " anterior " hæmorrhages were all septal and occurred almost exclusively in the younger age groups. The " posterior " hæmorrhages all occurred from the lateral nasal wall, and were mainly in older patients. The youngest in the latter group was 45 years of age, the oldest 82.

Therapeutic Measures

In the first instance the bleeding was controlled by " packing " or cauterization of the bleeding area. All patients, who showed a deficiency of Vitamin C and/or Vitamin K were given the necessary vitamins. The patients were given 200-300 mgm. ascorbic acid daily according to the degree of deficiency found and 15 mgm. of a Vitamin K compound for the period of 4 weeks.

Only 5 out of the patients returned with a recurrence of epistaxis. One of the patients had a cold recently and the bleeding probably started as a result of excessive " blowing ". The second patient had a fracture of the nasal bones, the result of a blow on his nose. The ascorbic acid levels and prothrombin time were normal in the 2 patients at this examination, whereas in the previous examination the amounts of Vitamin C and prothrombin were deficient. In the remaining 3 it was found that the subclinical deficiencies of Vitamin C and Vitamin K were still present, although to a lesser degree, than at the first examination. It could not be established with certainty whether they had carried out the prescribed treatment.

Twelve months after the conclusion of this investigation a letter was sent to the patients asking them to state whether they had any further nasal hæmorrhages. Of the 100 patients written to only 46 replied. Of these, 3 patients have had only one attack and 2 patients had several recurrences. Unfortunately none of the patients reported for re-examination.

Comment

The study of wound healing has been the subject of much thought through the ages, but it is only in recent years, that surgeons have become acquainted with tangible evidence concerning the value of certain systematically acting biochemical factors. Both clinical and laboratory observations have shown conclusively that the rate and efficiency of primary wound healing depend to a certain extent upon the Vitamin C content and the protein concentration in the tissues and to a lesser degree on the KH and some mineral metabolism. It must be remembered that the human organism cannot synthesize Vitamin C. Thus, since wound

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healing may be regarded as something of a body emergency, it is logical to expect that reserves of necessary substances in the body will be mobilized in any such exigency. Lauber and Rosenfeld (1948) in histological studies of the amount of Vitamin C in the body of guinea-pigs on low Vitamin C diet found that when healing of wounds was in progress there were diminished amounts of Vitamin C in the various tissues. They concluded that the apparent decrease was due to its utilization in the healing process.

It was Jeney and Törö (1936) who in their experiments added ascorbic acid to the nutrient medium of a culture of fibroblasts *in vitro* and observed a marked increase in the number of collagen fibrils. By this finding the basis was laid for an advance in the treatment of wounds. Since the repair and the strength of wounds in soft tissues are direct functions of a proliferation of fibroblasts and the formation of collagen, it is evident that Vitamin C plays an important part in the phenomenon of wound healing. It is shown by these experiments that a systemic deficiency of Vitamin C producing a scorbutic or prescorbutic state definitely affects wound healing and the strength is diminished. Bartlett (1942) found the tensile strength to be directly proportionate to the Vitamin C content of the scar tissue tested. Another striking effect is the retardation of the formation of new blood-vessels in the organization of lesions. In advanced scurvy all deposition of collagen and other intercellular material ceases. If the scurvy is interrupted by supplying the experimental animals with adequate amounts of ascorbic acid, deposition of collagen promptly resumes.

" Symptomatic " scurvy is not a condition frequently encountered among out-patients. Laboratory tests disclose a far greater incidence of " asymptomatic " scurvy than hitherto could be recognized by the usual methods of clinical examination. The term " asymptomatic " scurvy* existing in a patient without characteristic symptoms, physical signs or roentgenological evidence, but in whom the presence of a subscorbutic state may be determined by a chemical investigation and by the histological evidence of inferior granulation tissue.

If the daily intake of ascorbic acid falls below the minimal protective dose, the consequences of this increasing deficiency, after depletion of the body deposit become evident. Changes affected by a complete scorbutic diet of short duration can be reduplicated in humans by administration of a sub-standard dose over a long period of time. It seems logical to conclude, that the effect of this deficiency may be more widespread in our population than is generally realized.

King (1936) in a number of papers supported the view that Vitamin C plays some part in detoxication processes. Further chemical study of the

*May be defined as scurvy.

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relationship of ascorbic acid to toxins has led him to the conclusion that " in all cases the effect was shown by a real chemical combination between Vitamin C and the poison ". Ruskin and Jennard (1938) confirmed the findings of King when following a series of experiments they concluded that Vitamin C is in some way intimately concerned in the formation of serum protein complexes and that this combination is probably responsible for the detoxifying properties of ascorbic acid. All the investigators concluded that complete saturation aided greatly in diminishing infection in healing wounds.

No definite cause can be advanced for the diminution of prothrombin in 40 per cent. of the patients investigated. This factor is formed in the liver under the influence of the fat-soluble thermostable Vitamin K and it is an established fact, that deficiency of Vitamin K leads to hypoprothrombinæmia. This may be due to insufficient intake of Vitamin K in the diet as seen in malnutrition or in babies in the first days of life, when an insufficient amount of Vitamin K in the diet leads to melæna neonatorum. Assuming a normal intake of Vitamin K in the diet diseases interfering with the normal absorption of Vitamin K from the intestine will produce a prothrombopenic state. If there is disease of the liver parenchyma there will be deficient utilization of Vitamin K. Large doses of acetyl-salicylic acid may produce a state of prothrombopenia.

None of the above mentioned causes could be found in our series of patients but there may be causes for the production of hypoprothrombopenic states, which are still unknown. In analogy to the " subscorbutic " state, this entity may be termed " subclinical prothrombopenia ", which is less likely to have been brought about by a complete deprivation of Vitamin K in the diet, as due to an insufficient supply of Vitamin K in the food over a prolonged period. It is conceivable that Vitamin C, by its detoxifying effect, will counteract many an agent, which has a prothrombopenic effect on the human body, as it does counteract, given in large doses, the prothrombopenic effect of acetyl-salicylic acid and dicoumarol.

In Little's area two types of epithelium meet, the squamous as continuation of the skin and the columnar epithelium of the nasal cavity. It is accepted that erosions and ulcers in similar border areas in any part of the body heal more slowly. This may be considered as another " endogenous " factor operative in the delayed wound healing in Little's area.

Summary

In order to appraise the significance of Vitamin C, prothrombin, serum-calcium, clotting time and bleeding time as ætiological factors in nasal hæmorrhage, a hundred patients were examined by the biochemical methods mentioned. An attempt was made to correlate the findings with the attacks of bleeding and therapeutic measures were

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taken to evaluate the merits of ascorbic acid and/or Vitamin K in removing or decreasing the incidence of hæmorrhage.

It is not thought that the deficiency of Vitamin C and/or Vitamin K *per se* are the cause of the epistaxis, but one is led to believe that superimposed on an underlying ætiological factor, the deficiencies may increase the frequency of nasal bleeding and add to their severity.

The most significant aspect of this study is its possible bearing on states of partial deficiencies of Vitamin C and Vitamin K, brought about by insufficient supply of them over a prolonged period.

Both ascorbic acid and prothrombin time were normal in 20 per cent. of the patients. The ascorbic acid level was subnormal in 70 per cent. : 40 per cent. exhibited a hypoprothrombinæmia ; 7 per cent. showed a prolonged clotting time. Serum-calcium and bleeding time were normal in all cases. There were 67 " anterior " and 33 " posterior " hæmorrhages.

The experimental studies were mentioned by which it was proved that ascorbic acid promotes the formation of collagen and also has a detoxifying effect. The persistence of thrombi and lack of organization in Dohlman's cases could possibly be explained in this light. The bordering of squamous and columnar epithelium in Little's area may be looked upon as another possible " endogenous " cause.

The extremely high incidence of ascorbic acid and prothrombin deficiency and the gratifying clinical results attending the administration of ascorbic acid and/or Vitamin K suggest that Vitamin C and Vitamin K have a definite place in the management of nasal hæmorrhage.

Because of lack of co-operation on the part of the patients the correlation of laboratory findings and clinical course could not be achieved, as one would have wished.

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