LONG-TERM TREATMENT OF EPISTAXIS WITH OESTROGENS

BY

E. K. BLACKBURN, M.D., M.R.C.P.(Glasg.)

Haematologist, the Royal Infirmary and Royal Hospital, Sheffield

The object of this paper is to report the long-term efficiency of relatively low doses of oestrogens in the treatment of severe epistaxis in a brother and sister suffering from hereditary haemorrhagic telangiectasia and in a patient with maxillary sinusitis unassociated with hereditary disease.

Case 1

A colliery deputy aged 46 was referred on April 12, 1954. Bilateral epistaxes on alternate days had inconvenienced him increasingly in spite of repeated cauterization of the nose. At the age of 30 local radium treatment to telangiectases of the cheeks had been successful in controlling bleeding therefrom. This has remained effective over the last 24 years. His father, paternal cousin, one of his three brothers, and one of his four sisters (Case 2) have also suffered from the hereditary disease.

On examination typical telangiectases were noted on the cheeks, lips, ears, tongue, fingers, and toes of the left foot. The haemoglobin level was 73% and the blood film showed evidence of iron deficiency.

On May 3 daily oral treatment with 0.5 mg. of ethinyl-oestradiol, and with 5 mg. of methyltestosterone to counteract the feminizing effects of the former drug, was instituted. During the eight years which have passed since then he has had very slight epistaxes on three occasions only, associated with coryza and bronchitis. As he complained of pain and fullness in the region of the nipples on May 31 the combined hormone therapy was given on alternate days for five weeks, then every four days for two weeks, and finally once weekly. The symptoms referable to the breasts disappeared in six weeks. On February 3, 1958, he told of nausea (once accompanied by vomiting) following the three previous occasions on which he had taken the drugs. Sensitivity to ethinyl-oestradiol was diagnosed, and chlorotrianisene 12 mg. weekly was substituted for this drug. The methyltestosterone was stopped as there was no evidence of feminization. His gastric symptoms were completely relieved. The dosage of chlorotrianisene was reduced to 12 mg. every 10 days on June 30, 1958, and has been maintained at this level for four years.

Iron therapy was given during the first few months of hormonal treatment, since when it has not been necessary.

Case 2

A married woman of 59 was referred on September 17, 1956, with a history of epistaxes since the age of 20, when she first noticed spots on her face. For the past few weeks epistaxes had been more severe than ever before and had occurred two or three times a day. Examination revealed telangiectases on the buccal mucosa, tongue, lips, distal ends of the left thumb, right thumb, forefinger, and middle finger and of the right little toe. The haemoglobin level was 68%, and a blood film showed evidence of iron deficiency.

Treatment with 0.25 mg. of ethinyl-oestradiol daily was begun. Her nose bled only once a week during the next month, and throughout the succeeding five years she has had very slight epistaxes only when she has had a cold. After eight months the dosage of ethinyl-oestradiol was reduced to 0.25 mg. on alternate days. Eight months later, on March 31, 1958, she complained of a little loss of blood per vaginam. At operation a large ovarian cystadenoma burrowing into the broad ligament was found. Oophorectomy and hysterectomy were performed without complications; the shaginess of the uterine endometrium was thought to be due to the oestrogen therapy. The epistaxis being completely controlled, the dosage of ethinyl-oestradiol was reduced to 0.25 mg. every third day on June 30, 1958, and has been maintained to date (September 30, 1962).

Iron therapy was given at the outset, and the haemoglobin reached a normal level (102%) in four weeks.

Case 3

A housewife aged 65 was referred on April 27, 1959, because of severe epistaxes from the right nostril, the severity having increased gradually for four years. She suffered also from severe pain referable to the right maxillary sinus. Her nose had been cauterized frequently. On two occasions blood transfusion had been necessary. When aged 64 a benign polyp was noted in the right maxillary antrum and a Caldwell-Luc operation was performed. There was no additional history of abnormal haemorrhage in herself or family, covering five generations.

Examination revealed clinical evidence of anaemia, and a blood-pressure of 200/75. No telangiectases were detected. X-ray examination of the maxillary sinuses showed no residual opacity. The haemoglobin level was 65% and the blood film showed evidence of iron deficiency. Treatment with ethinyl-oestradiol 0.5 mg. daily was begun on April 27. Two small epistaxes occurred during the next week and only one in the succeeding six weeks. The dose of ethinyl-oestradiol was reduced to 0.05 mg. daily on June 15. No further epistaxes occurred, but on July 27 she bled per vaginam. Between this date and September 19, 1960, the dosage of oestrogen was altered frequently with the object of eliminating epistaxis on the one hand and bleeding per vaginam on the other. A dose of 0.05 mg. ethinyl-oestradiol weekly has been effective in maintaining this state of affairs during the past two years, for which time she has been free of pains referable to the maxillary sinus. Iron therapy was given as indicated haematologically.

With standard methods no abnormality of blood coagulation or of platelets was found in the three patients.

Discussion

An extensive literature has grown up around the subject of hereditary haemorrhagic telangiectasia (Williams and Brick, 1955). Although telangiectases may occur in any blood organ, they are found most often on the nasal and oral mucosae. Treatment of the disease includes prophylaxis, the arrest of haemorrhage by such measures as nasal packing, and blood transfusions and iron therapy as required. Attempted eradication of the lesions with topical applications of caustic agents, with local injections of sclerosing agents, and with x-ray or radium therapy have been disappointing on the whole, but some good responses have occurred—for example, the effect of radium in Case 1. Although the local lesions may be destroyed readily by electrocauterization, near-by satellite lesions soon form. More desperate measures, such as ligation of the external carotid or anterior ethmoidal arteries, have usually had disappointing results.

Until the work of Koch, Escher, and Lewis (1952) no therapeutic approach had consistently decreased the incidence or severity of recurrent haemorrhages. These authors reported control of epistaxis for many months in five patients treated with oestrogenic hormone in large doses, varying between 0.25 and 1 mg. of ethinyl-oestradiol daily. The history of their Case 1 lay behind this rationale. Epistaxes occurred one to five days before the end of the secretory phase of the endometrium and disappeared shortly after the onset of menstruation. After x-ray castration they became acyclic and increased in severity. Hence epistaxes

were related to periods of decreased oestrogen excretion. Ethinyloestradiol was the therapy chosen in view of its close relationship to α -oestradiol.

Undesirable side-effects of oestrogen therapy include sodium and water retention and urticaria in both sexes, oestrogen withdrawal-haemorrhage in the female, and gynaecomastia in the male. There is also the risk of producing mammary or uterine carcinomata. Oral oestrogen therapy may cause anorexia, nausea, and rarely vomiting as in our Case 1.

Harrison (1956) described the cases of four patients with hereditary haemorrhagic telangiectasia who had been under high-dosage oestrogen treatment (0.25–1 mg. ethinyloestradiol daily) for six to nine months and in whom the telangiectases had virtually ceased to bleed. As noted in the present Cases 1 and 2, he found no macroscopic evidence of any changes in the telangiectases after oestrogen therapy, but in two cases sections of tissue from the inferior turbinates taken before and after treatment showed that the normal columnar epithelium had changed to a squamous one. He suggested that in this way the telangiectases may be protected from trauma.

In view of the potential dangers of prolonged administration of large doses of oestrogens it is probably wise to restrict such treatment to women after the menopause and to men after the male climacteric. Relatively small doses of oestrogen compared with those used by Koch *et al.* (1952) and by Harrison (1956) controlled the haemorrhage in the present three patients, and such relief appeared to be perfectly justifiable. Our Case 1, previously responding well for three and a half years to 0.5 mg. of ethinyloestradiol weekly, is well controlled on 12 mg. of chlorotrianisene every 10 days, Case 2 with 0.25 mg. of ethinyloestradiol every three days, and Case 3, not suffering from the hereditary disorder, with 0.05 mg. of the latter drug weekly.

The effects of stopping oestrogen therapy and of starting it again have not been determined. So far these measures have appeared to be clinically unjustifiable.

Summary

The apparent success of oestrogen therapy in the long-term control of severe epistaxis in two patients suffering from hereditary haemorrhagic telangiectasia and in one patient suffering from local nasal disease only is reported. Much smaller doses than those previously recommended have been used for maintenance therapy.

The precise mechanism of the effect of oestrogen is at present unknown.

I am indebted to Mr. H. Petty, Mr. A. Young, and Dr. H. Wilkes for referring their cases; to colleagues for their reports; and to Dr. H. T. Swan and Dr. J. R. Tighe for reading the manuscript.

REFERENCES

- Harrison, D. F. N. (1956). *Guy's Hosp. Rep.*, **105**, 246.
Koch, H. J., jun., Escher, G. C., and Lewis, J. S. (1952). *J. Amer. med. Ass.*, **149**, 1376.
Williams, G. A., and Brick, I. B. (1955). *Arch. intern. Med.*, **95**, 41.

"I do wish, most sincerely, that the humble little man who cleans a lavatory could be made to realize how much genuine pleasure he gives, and how much genuine good he does, by really well done work," said Dr. A. Robinson, assistant medical officer of health of the City of London, in a lecture on hygiene in offices and shops sponsored by the Royal Institute of Public Health and Hygiene. He went on to remark that "a lavatory must not only be clean, but must be seen to be clean."

Medical Memoranda

Use of Arteriovenous Shunt for Haemodialysis in 8-months-old Infant

The use of an exteriorized indwelling arteriovenous shunt in haemodialysis was first described by Quinton *et al.* (1960). A 4-year-old infant was the youngest patient in whom these cannulae have been used (Hegstrom *et al.*, 1961).

This paper reports the use of an arteriovenous shunt in an 8-months-old infant, details some aspects in its insertion, and describes the particular model designed and adapted for use in infants.

The salient clinical features are as follows. After gastrointestinal symptoms of one week's duration, the infant attended hospital with uraemia, thrombocytopenia, and marked fragmentation of the red blood cells. A diagnosis of red-cell fragmentation syndrome of childhood was made. The serum-electrolyte levels are given in the Table.

Serum-electrolyte Levels

	Before Dialysis	After Dialysis
K ⁺	5.4 mEq/l.	4.3 mEq/l.
Na ⁺	120 "	135 "
Cl ⁻	87 "	98 "
Bicarbonate	9 "	17 "
Protein	12 "	14 "
Haematocrit	22%	33%
Urea	285 mg./100 ml.	120 mg./100 ml.

VESSELS CANNULATED

The cannulae were inserted into the brachial artery and basilic vein at the level of the elbow-joint. The calibre of the vessels at this level enabled the insertion of cannulae large enough to ensure adequate blood-flow rates during

FIG. 1.—By-pass shunt with threaded male luer-lok fittings. The flared terminal ends of the shunt which prevent the fittings from slipping off are shown. The reciprocal female luer-lok fittings of the vessel cannulae are evident in the lower part of the figure.

haemodialysis. At this level the arterial anastomosis around the elbow-joint is sufficient to maintain the distal arterial supply, despite ligation of the brachial artery.

Under local anaesthesia, the vessels were explored through a single vertical incision medial to the biceps