"PREMARIN" AS A HAEMOSTATIC AGENT: FAILURE TO DEMONSTRATE ANY LABORATORY OR CLINICAL EFFECT

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"Premarin" is a complex of oestrogen sulphates prepared from the urine of pregnant mares. During recent years it has been widely used as a haemostatic agent mainly in controlling epistaxis, but also in surgery, particularly on the prostatic gland.

Jacobson (1941) introduced the term "spontaneous bleeding," by which he understood any bleeding without a known cause such as trauma, surgery, tumours, ulcers, haemorrhagic diathesis, and so on. He believed this kind of bleeding to be a clinical entity, which was caused by a low oestrogen level in the blood, and postulated that premarin might arrest such bleeding.

The experimental support for the use of premarin as a haemostatic agent was offered by Johnson (1957). He injected premarin into 12 dogs, and 15 to 30 minutes later he found an increase in prothrombin and proaccelerin (factor V), and a decrease of antithrombin. The effect lasted for several hours. He concluded that "an elevation [of factor V] might be of importance for the prevention or control of bleeding. Should human plasma have a rise in Ac-globulin [that is, factor V] values following oestrogen administration proportional to that in the dog, this would be of unusual advantage to man."

During recent years several clinical reports have appeared, almost all claiming a favourable effect of premarin as a haemostatic agent. Apparently more than one million injections of premarin have been given, and no side-effects have been reported.

Jacobson (1954, 1955) reported that oestrogen therapy alone arrested bleeding in more than 300 cases of epistaxis, and in about 100 cases of various types of haemorrhages, particularly delayed post-tonsillectomy haemorrhage, rectal bleeding, gastro-intestinal bleeding, and subarachnoid haemorrhage. Menger (1955)

reported a dramatic response to premarin in all of 16 cases of spontaneous epistaxis and haemorrhage after adenoidectomy. Rigg (1957), using premarin in ophthalmology and otolaryngology, stated that "there is no doubt in my mind that the amount of bleeding during surgery and the incidence of excessive bleeding post-operatively have been markedly reduced." Hall and Ursin-Holm (1959) found that premarin controlled the bleeding in 17 out of 26 patients with epistaxis and bleeding after tonsillectomy, and concluded that oestrogen therapy probably had an effect. Bleeker (1959) reported a striking effect in epistaxis and in surgery on the prostatic gland. Cooner and Burros (1960), in a double-blind study, could not demonstrate any haemostatic effect of premarin in prostatectomy.

We were asked by Nyegaard & Co., Oslo, Norway, to advise them whether premarin should be marketed in Norway. We felt that the theoretical concept of "spontaneous bleeding" was unsound, that the laboratory experiments could hardly explain the reported clinical effects, and that all clinical studies claiming good effect lacked adequate control groups. The following study was therefore undertaken.

Materials and Methods

Premarin, 20 mg. per phial, has been used for intravenous administration.

A placebo was prepared for intravenous administration by Nyegaard & Co.

Effect on the Haemostatic Mechanism in Normals.—In eight normal individuals (four men and four women) various tests on the haemostatic mechanism were carried out before and at intervals after an intravenous injection of 20 mg. of premarin. References to methods are given in Table I.

Effect on Abnormal Bleeding-time and Tourniquet Test.—The bleeding-time and the tourniquet test were tested before and one hour after intravenous injection of 20 mg. of premarin. The tourniquet test was performed according to the method of Stefanini and Dameshek (1955).

Effect on Blood Loss After Prostatectomy.—Thirty-one patients with benign adenoma of the prostatic gland who were operated on according to the method of Harris (1929) (Andersen, 1957) by the same team of surgeons, were given 20 mg. of premarin intravenously half an hour before the operation started. Twenty of them had another injection six hours after operation. The blood loss during operation and on each post-operative day was measured as haemoglobin in a Klett-Summerson photoelectric colorimeter and converted to millilitres of blood as the haemoglobin of the patient's blood was known. A sucker was used extensively at operation, and the blood was collected in the suction bottle. The contents of this bottle were diluted with distilled water

TABLE I.—Effect of Premarin in Normals. Mean Value of Various Tests for Haemostatic Functions in Eight Normals Before and After 20 mg. of Premarin Intravenously

	Before Premarin	After Premarin			Normal Range	Reference for Methods
		½ Hour	1½ Hour	3 Hours		
Whole-blood clotting-time (min.)	3½	3½	4	3½	2-5	Hjort and Stormorken (1957)
Bleeding-time (min.)	5	5	5½	5½	2-11	Borchgrevink and Waaler (1958)
One-stage prothrombin test (sec.)	14.7	14.8	14.6	14.7	13-15	Quick's test using human brain thromboplastin
Cephalin time (firm clot formed) (sec.)	57.0	57.9	58.3	57.3	50-60	Waaler (1957)
P and P test (%)	100	100	102	99	75-130	Owren and Aas (1951)
Prothrombin (%)	100	99	101	98	75-130	Hjort <i>et al.</i> (1955)
Proaccelerin (factor V) (%)	100	102	104	104	70-140	Aas (1952)
Platelet count ($\times 1,000$ c.mm.)	248	254	240	246	150-350	Nygaard (1933)
No. of adhesive platelets (% of total)	41		44		30-60	Hellem (1960)

* Sensitive to Stuart factor (factor X).

to 10 litres for haemoglobin estimation. The swabs used were soaked in water, and the amount of haemoglobin was determined. The 24-hour urine was collected for each of three days, and haemoglobin was measured. This group of patients was compared with another group of 40 patients of the same age and with the same diagnosis, operated with the same technique, but without premarin therapy. Half of this group were operated on just before and half just after the premarin study. To the best of our knowledge the two groups were equal in all relevant respects, except for the premarin.

Effect on Epistaxis.—Eleven patients with severe epistaxis of more than four hours' duration, without hypertension and without haemorrhagic diathesis, were at random given either placebo intravenously or premarin 20 mg. intravenously. If necessary, the dose was repeated after one hour. Neither the patient nor the doctor knew whether the particular patient had received placebo or premarin.

Results

Table I shows the result of various tests for haemostatic functions in normals before and after premarin injection. Obviously no change took place within three hours after the injection.

Table II shows that 20 mg. of premarin intravenously had no shortening effect on the prolonged bleeding-time in patients with von Willebrand's disease or with

TABLE II.—*Effect of Premarin in Patients with Prolonged Bleeding-time*

Sex	Age	Diagnosis	Bleeding-time in Minutes		Platelet Count (per c.mm.)
			Before Premarin	1 Hour after 20 mg. Premarin Intravenously	
M	56	von Willebrand's disease	>30	>30	253,000
F	44	Cirrhosis	>30	>30	40,000
F	63	Pancytopenia	>30	>30	10,000
F	27	I.T.P.	30	28	78,000
M	33	Leukaemia	>30	>30	1,200

TABLE III.—*Effect of Premarin in One Patient with von Willebrand's Disease. Bleeding-time and Tourniquet Test in a 56-year-old Man Before and During Premarin Treatment, 20 mg. Intravenously Twice Daily*

	Before Treatment	Days on Treatment			
		5	6	10	12
Bleeding-time in minutes	>30	>30	>30	>30	>30
Tourniquet test, No. of petechiae	20-30	15-20		20-30	

TABLE IV.—*Effect of Premarin on a Positive Tourniquet Test*

Sex	Age	Diagnosis	No. of Petechiae	
			Before Premarin	1 Hour after 20 mg. Premarin Intravenously
M	56	von Willebrand's disease	15-20	30-40
F	63	Pancytopenia	30-40	25-35
M	33	Leukaemia	100-120	80-100

thrombocytopenia of various causes. Nor did premarin twice daily for more than a week have any shortening effect on the bleeding-time in a patient with von Willebrand's disease (Table III). Table IV shows that a pathological tourniquet test remained unchanged after the injection of premarin.

Table V gives the results in prostatectomy. Mean, medium, and range have been recorded and no significant difference can be demonstrated between the groups. It is in fact more striking that the two groups are so similar. Blood transfusion was not necessary during operation, and only one patient, in the control group, needed 500 ml. on the second post-operative day.

Table VI shows the result of the small double-blind study in epistaxis. The placebo preparation was as effective as premarin in controlling the bleeding.

Discussion

Johnson (1957) found an increase in prothrombin, factor V, and a decrease in antithrombin after injections of premarin. It is not obvious to us that such an increase would be beneficial to patients. Patients with spontaneous bleeding are said to have normal coagulation (Jacobson, 1955), and there is no proof that an increased concentration of clotting factors leads to more efficient coagulation. Furthermore, if a hypercoagulable state were produced, it is not at all certain that this would be an advantage. Haemostasis in small vessels depends mainly on platelets and vascular factors, not on coagulation (Zucker, 1947). Therefore, hypercoagulability may not be able to stop diffuse bleeding. On the other hand, hypercoagulability may well be dangerous, leading to thrombotic processes and consequently a reduction in platelets, prothrombin, proaccelerin (factor V), and antihæmophilic A factor (factor VIII); in other words, an increased bleeding tendency might hypothetically be the result of the therapy. We admit that all this is speculation, but not necessarily less valid than the speculation which has been marshalled in favour of premarin.

Johnson worked with dogs, and we failed to confirm his results for prothrombin and factor V in man. Thus, if hypercoagulability is a useful therapeutic achievement, this argument can be valid only for dogs. Our findings have been confirmed by Nilsson (1960).

We could not demonstrate any effect of premarin in patients with hæmorrhagic diathesis. This is, however, not surprising, since premarin is said to have effect only in "spontaneous bleeding," which excludes

TABLE VI.—*Cessation of Bleeding Within One Hour After One Injection (if Necessary Two Injections) of Premarin or Placebo into Patients with Epistaxis*

	No. of Patients	Cessation of Bleeding within 1 Hour	
		Yes	No.
Premarin	6	2	4
Placebo	5	2	3

TABLE V.—*Blood Loss in Prostatectomy*

	No. of Patients	Average Age	Blood Loss in ml.											
			During Operation			Rest of 1st Day			2nd Day			3rd Day		
			Mean	Median	Range	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Without premarin ..	40	68½	122	104	24-286	127	95	16-508	61	43	8-200	52	37	6-258
Premarin*	11	70	123	122	30-222	124	112	42-258	67	39	18-164	52	34	10-174
Premarin†	20	67				131	68	8-425	57	42	8-168	51	26	0-266

* 20 mg. intravenously half an hour before operation. † 20 mg. intravenously half an hour before and same dose 6 hours after operation.

haemorrhagic diathesis as a cause of the bleeding (Jacobson, 1941).

Even if we could not show any effect on the haemostasis in normals, premarin might well act as a haemostatic agent clinically, through some as yet unknown mechanism. We chose to test this out in epistaxis and in surgery on the prostatic gland, two conditions in which the effect of premarin has been reported to be excellent.

We could not confirm the results of Bleeker (1959), who found that in prostatectomy the number of blood transfusions could be reduced by 50% when premarin was used. There can be no doubt that if premarin is given in surgery the evaluation of the effect should be done with a blind technique. If this cannot be done, it must be preferable to measure the actual loss of blood as in this study, rather than to rely on changes in haemoglobin values or impressions of the blood loss. There was no difference in blood loss between patients who received premarin, either preoperatively only or both pre- and post-operatively, and those who did not receive premarin. Our findings are in good agreement with the result of the double-blind study of Cooner and Burros (1960).

In this connexion we would like to point out that, according to Jacobson, "spontaneous bleeding" excludes surgical and traumatic bleeding. Therefore there should be no indication for premarin therapy in such cases.

Jacobson (1954) states that "spontaneous bleeding" is often preceded by tension or stress. One may assume then that the bleeding in itself will increase the anxiety and a vicious cycle will then be started. All kinds of treatment which would tend to break this cycle somewhere will reduce the actual bleeding. This should be kept in mind when the effect of premarin in epistaxis is evaluated. When a physician takes care of such a patient, talks with him, puts him to bed, gives him any kind of medicine, he will calm the patient and tend to break the cycle. This treatment in itself would be a major factor in controlling the bleeding. If premarin has any effect over and above this, it must be proved in a controlled study with a double-blind technique. This has never been done, and the clinical reports on premarin are therefore of little value in our opinion. Our double-blind study is unfortunately small, but it does suggest that the effect of premarin is only that of a placebo.

The theory that "spontaneous bleeding" is a clinical entity which is due to a low oestrogen level in the blood seems to us to be very speculative and loosely founded. So far as we know, this postulated low level of oestrogen has never been demonstrated. If the theory be correct, it is difficult to understand why there is not a striking difference in the incidence of spontaneous bleeding between men and women.

We have confirmed that premarin produced no side-effects. We think, however, that this fact in itself is no justification for the extensive use of premarin. We are afraid that such a drug will give the doctor who is using it a false sense of security, and that this, together with the additional expense, is against the best interest of the patient.

Summary and Conclusion

The haemostatic effect of premarin has been tested on: (1) various vascular, platelet, and clotting functions in normal individuals; (2) prolonged bleeding-time and

positive tourniquet tests in patients with haemorrhagic diathesis; (3) patients undergoing prostatectomy: blood loss during operation and for the next three days has been measured, and compared with the loss in a control group; and (4) patients with epistaxis; in a double-blind study.

In the first three groups no effect, and in the fourth a placebo effect only, could be demonstrated.

Premarin produced no side-effects. Still, the danger of false security by using an ineffective haemostatic agent should not be underestimated.

As a result of this study, premarin has not been marketed in Norway.

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SCHOOLGIRLS' BEHAVIOUR AND MENSTRUATION

BY

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The possibility of girls' behaviour being adversely affected by menstruation has been discussed in a previous paper (Dalton, 1960), in which the deleterious effect of menstruation on school work was analysed. An excellent opportunity of studying their behaviour presented itself at an English public school. Here it is the custom for all order marks given for bad behaviour to be recorded together with the date and type of offence, and it is also customary for the matron to keep records of the girls' menstruation dates. This paper analyses offences committed during the spring term of 1960.

The school is situated in the Home Counties, occupies over 400 acres, and boards 350 girls between the ages of 8 and 19 years. The school aims to prepare girls "for the dual role of home-maker and professional woman, special attention being given to their moral and religious training." There is a preparatory school for girls between 8 and 11 years; the senior school is