Capillary strength of women with menorrhagia

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IT HAS been shown[1, 2] that the capillary strength of the skin of the arm usually falls briefly after ovulation and more markedly before normal menstruation. It is therefore pertinent to question whether women with regular menorrhagia might not show more pronounced changes of capillary strength, and also whether substances such as ascorbic acid and the bioflavonoids, known to fortify capillaries, might not prove useful in the treatment of menorrhagia. The present investigation was carried out in order to answer these questions.

Method

Capillary strength was determined as previously described,[1] using a simple suction petechiometer. This instrument has been tested by Brown[3] against a modified Dalldorf resistometer, and only 10 per cent of his patients showed readings by the two instruments which differed by more than 5 cm. Hg.

All patients in this study had heavy menstrual losses and fairly regular cycles, without demonstrable pelvic disease. The majority had been admitted to the hospital for investigation and curettage, but the phases of the menstrual cycle at which they had been curetted were variable. Whenever possible in this study, at least 1 month was allowed to elapse after the curettage before daily studies of capillary strengths and basal body temperatures were commenced. The women took their own rectal temperatures before arising in the morning, but the capillary strength determinations were all done by one observer (L. M. B.), who visited them in their homes 6 days each week for several months.

At first, pad saturation counts were used to estimate the menstrual blood loss, but later many of the women wore Tassette intravaginal rubber cups to collect the blood and plastic measuring cups were used to measure it. After using both techniques, we estimated that 10 c.c. of menstrual blood was equivalent to one soaked pad. All the women were studied for at least one cycle before treatment was started. In the first year of study there were not enough patients for a controlled series, and all of the women were given the test capsules containing water-soluble citrus bioflavonoids and ascorbic acid, 1 capsule three times a day. In the second year of study alternate patients were given control (lactose) capsules or test capsules, 1 capsule three times a day for 2 months or longer before changing each patient to the opposite capsules. Originally this project was planned to be a double-blind study, but the aroma of the test capsules soon disclosed to the investigators which capsules were which. However, since both the capillary strength and the blood losses were measured objectively, this knowledge could not have influenced the eventual results.

There were originally 52 women included in this study of menorrhagia, but 9 of them improved spontaneously after curettage, and

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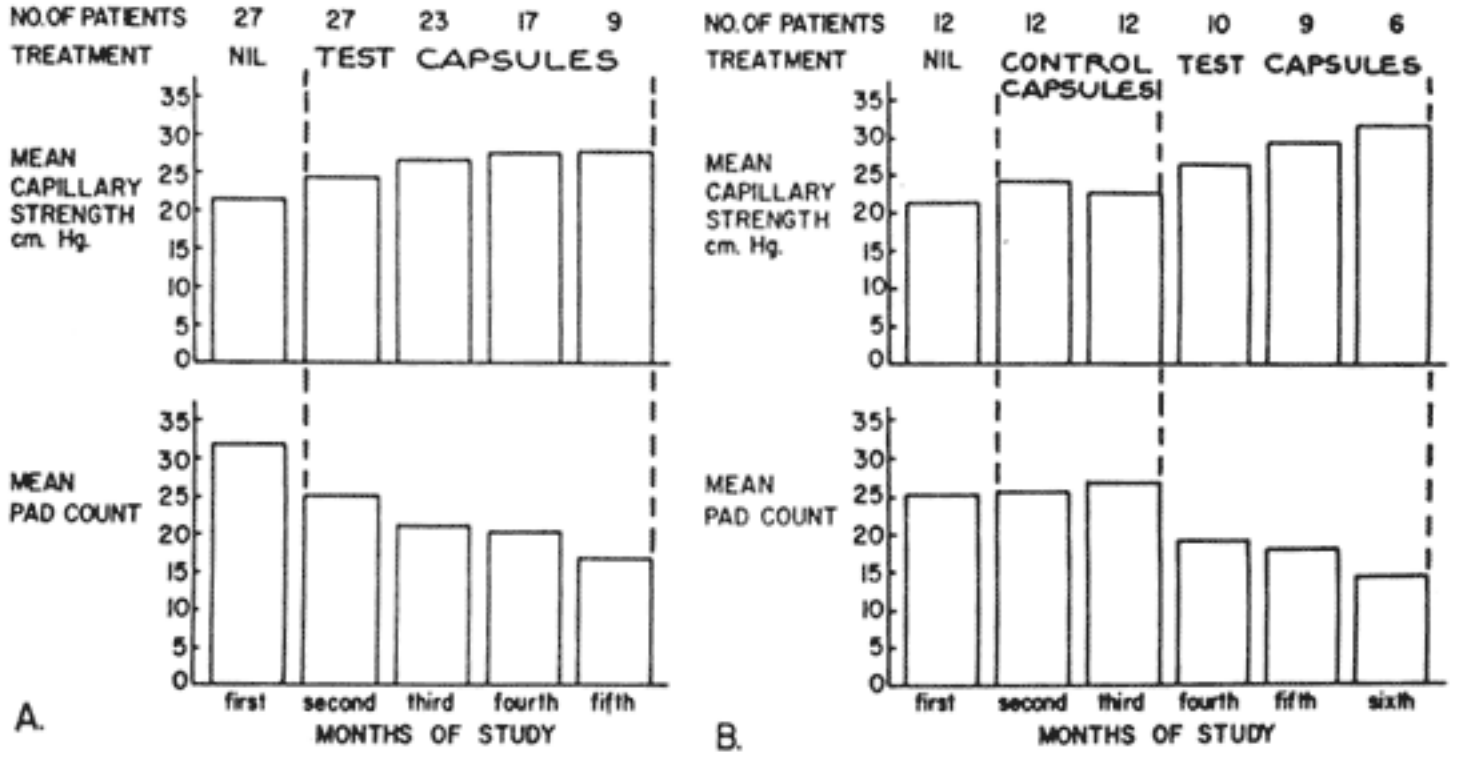

Fig. 1. Block graphs illustrating average menstrual blood loss and monthly mean capillary strengths of women with menorrhagia, before and during treatment with water-soluble citrus bioflavonoids and ascorbic acid. *A,* Twenty-seven women observed for one complete menstrual cycle and then treated with test capsules showed elevation of mean capillary strength and progressive reduction of average blood loss. *B,* Twelve women observed for one complete menstrual cycle and then treated with control (lactose) capsules for 2 months showed little change in capillary strength or blood loss until test capsules were substituted for control capsules.

Table I. Comparative analysis of effects of 2 months' treatment with "A" control capsules and "B" test capsules on women with menorrhagia*

	Second month on control capsules	*Second month on test capsules*	*Third month on test capsules*	*Fourth month on test capsules*	
Increase in blood loss (%)					
70-80					
60-70	1	1		1	
50-60					
40-50					Worse
30-40			1		
20-30	3		1†	1†	
10-20	2	1†		1	
±0-10	6	3†	2		No change
Decrease in blood loss (%)					
10-20		4	2†	1†	
20-30		9	3		
30-40		6	3	3	
40-50	1	5	6	6	Better
50-60		3	9	4	
60-70		5	1	2	
70-80				2	
	6 worse 6 no change 1 better A	2 worse 3 no change 32 better B	2 worse 2 no change 24 better C‡	3 worse 0 no change 18 better D‡	

*It may be noted that while the majority of patients showed a good response to treatment, the 2 women with cystic hyperplasia of the endometrium were among those who did not show a satisfactory response.

†One of this number had cystic hyperplasia of the endometrium.

‡Results of third and fourth months of treatment with test capsules.

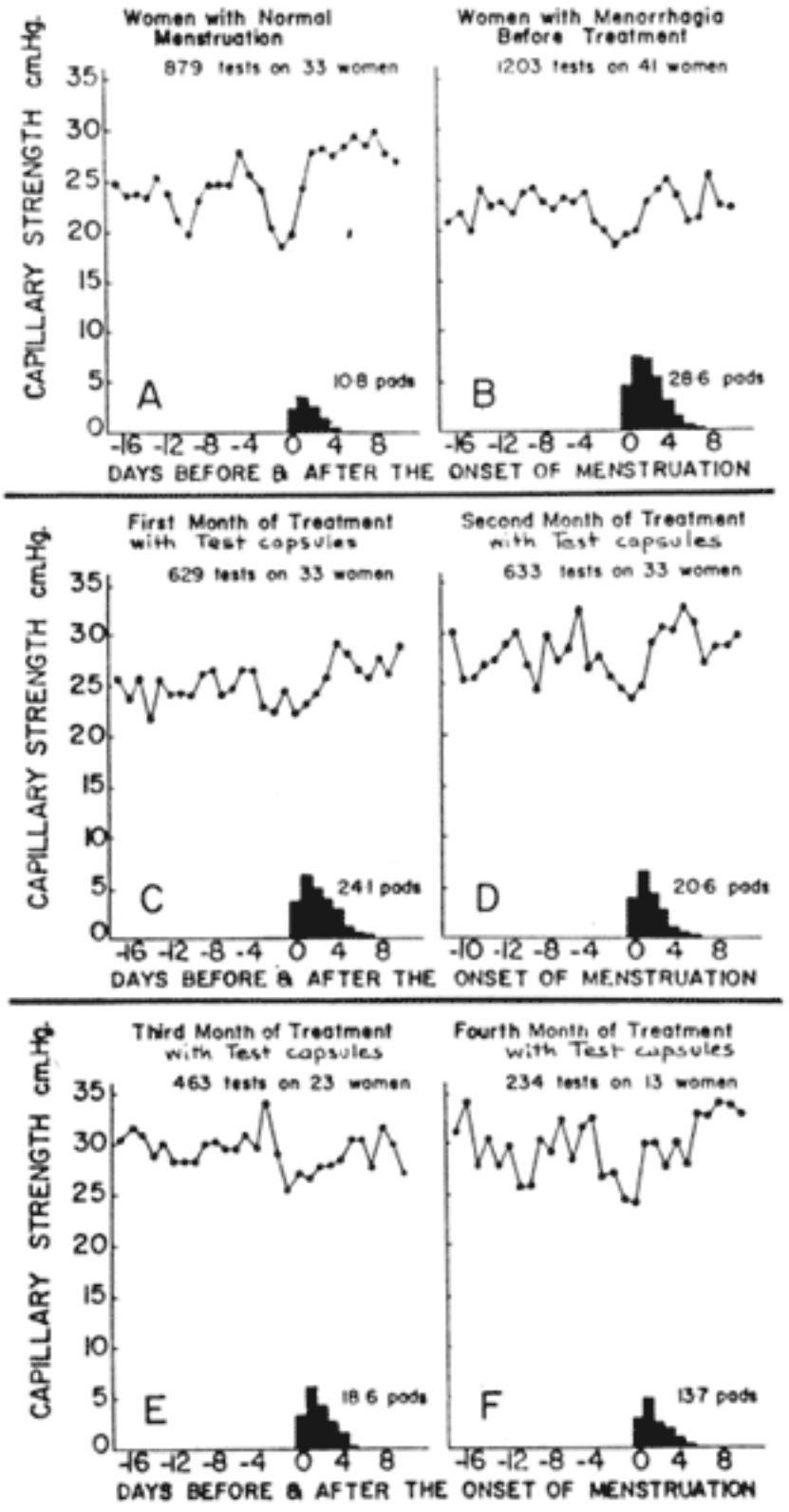

Fig. 2. Charts illustrating the means of daily capillary strength determinations. Menstrual cycles of all the women in each group are superimposed on one another at day of onset of menstruation, and other days are calculated as days before or days after onset of menstruation. *A,* Thirty three healthy women with normal blood loss of 10.8 pads per period; chart shows the normal postovulatory and premenstrual depressions of capillary strength. *B,* Forty one women with menorrhagia who had an average blood loss of 28.6 pads per period. Note that the average capillary strength of these women is lower than normal and that the normal pattern is not well shown. *C, D, E,* and *F,* Results obtained in the patients with menorrhagia during the first, second, third, and fourth months of treatment with test capsules. Capillary strength rose during treatment, and by the fourth month of treatment a relatively normal capillary strength pattern had returned.

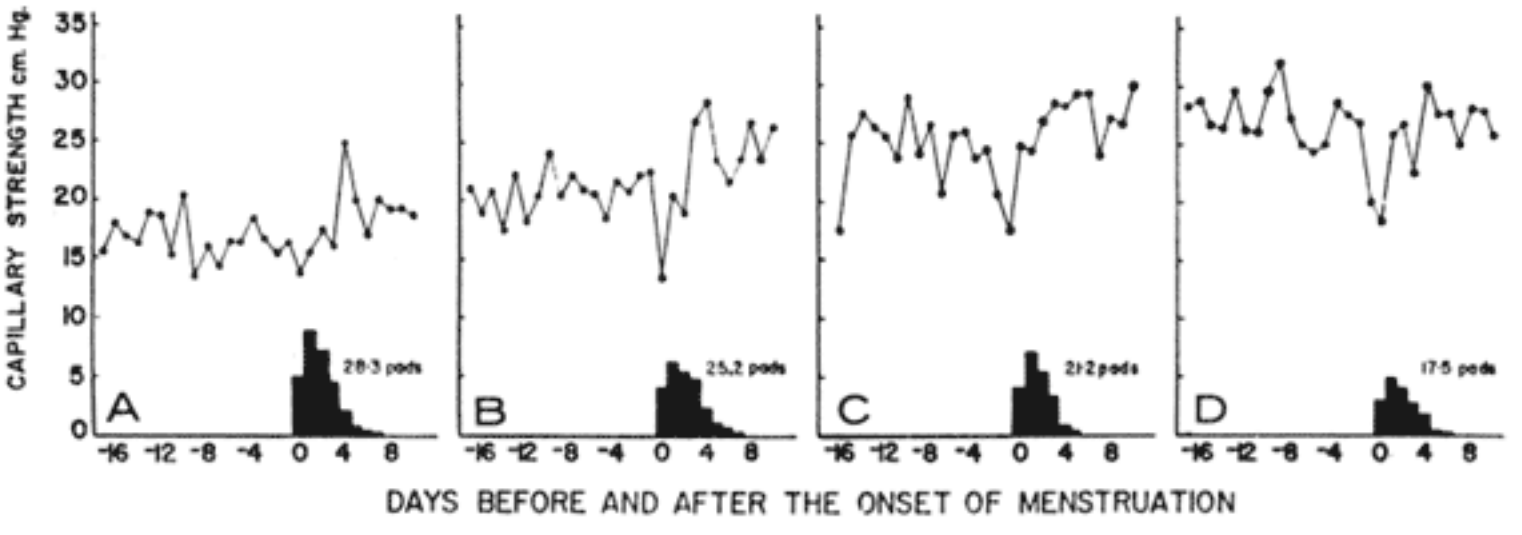

Fig. 3. Twelve women with menorrhagia whose capillary strength averaged less than 20 cm. Hg before treatment. *A,* Before treatment. *B,* First month on treatment with test capsules. *C,* Second month on test capsules. *D,* Third month on test capsules. Note that premenstrual drop of capillary strength was absent before treatment but became evident when the average capillary strength rose as a result of treatment.

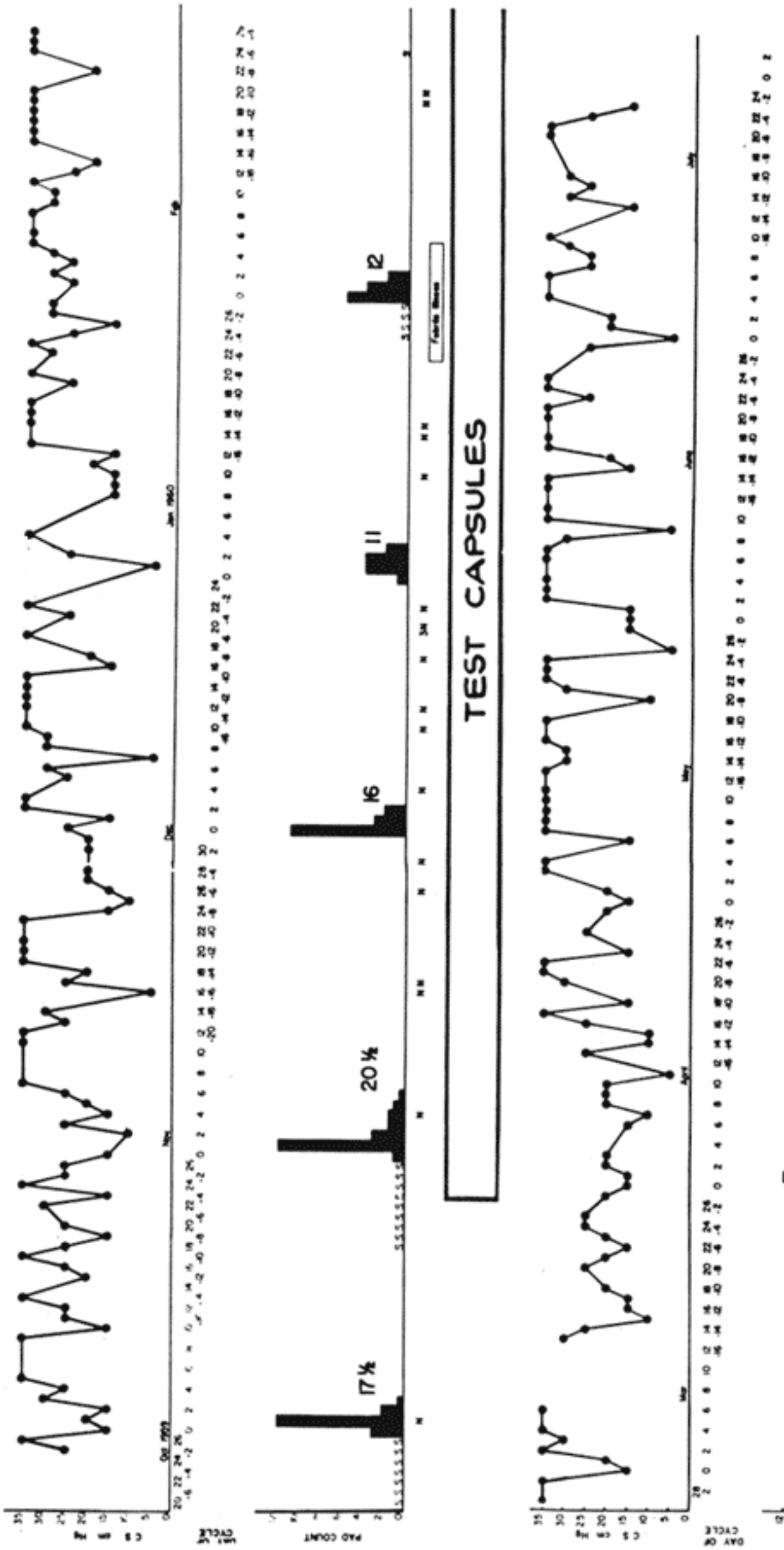

Fig. 4. Record of daily capillary strength of a 34-year-old woman who had excessive menstrual blood losses, indicated by black blocks; premenstrual spotting, indicated by the letters *S* above the base lines; and nosebleeds, indicated by the letters *N* below the base lines. Treatment with test capsules elevated capillary strength, reduced menstrual blood losses, and eventually reduced the frequency of the epistaxes, but did not affect premenstrual spotting.

their blood loss during the initial month of study, without treatment, was normal. These 9 were, therefore, excluded from all graphs and charts. This left 43 women with persistent menorrhagia whose capillary strength was studied daily, without treatment, for 1 month. Two women with cystic hyperplasia of the endometrium, which constitutes a separate problem, were excluded from all of the graphs, but they were included in Table I.

This left 41 women whose capillary strength was studied for 1 month without treatment; 37 of these were followed for 1 month on treatment, 33 for 2 months, 23 for 3 months, and 13 for 4 months on treatment, in addition to the initial month without treatment. Thirteen of the 41 women were studied for 2 months on control capsules after the initial month without treatment before being changed to the test capsules. An ideal study would have needed observation of more women for a longer period on control capsules, but both they and their personal physicians became dissatisfied when no improvement was evident, and several were lost from the series because of receiving hormone injections.

The total number of treated patients in Table I is slightly larger than that shown in other graphs and figures because pad saturation counts were known for several women who were not available for daily testing of capillary strength.

A comparison of the effects of 2 months of treatment with lactose capsules in 13 women with the results of 2 months of treatment with the test capsules in 37 women is shown in columns 1 and 2 of Table I. Thirty-two of the 37 women showed a decreased blood loss when treated with the test capsules, whereas only 1 out of 13 improved with lactose control capsules.

Similarly, a comparison of *A* and *B* in Fig. 1 shows a distinct elevation of capillary strength after 2 months of treatment with test capsules *(A)* which was not evident after 2 months of treatment with control capsules *(B)*. It may also be noted that the capillary strength of the women treated with lactose *(B)* did improve after they had been changed to treatment with test capsules.

Fig. 2, *A* shows the mean daily capillary strength pattern of 33 normal women with an average blood loss of 10.8 pads for comparison with Fig. 2, *B*, which shows the mean daily capillary strength pattern of the group of 41 women with menorrhagia, having an average blood loss of 28.6 pads per period before treatment. It may be noted that the mean capillary strength was somewhat lower than normal in the patients with menorrhagia and that the pattern was less distinct.

Most of these women with menorrhagia had shown evidence of ovulation, either by the findings of curettage or on their temperature charts, but some are included in whom such evidence is wanting. Fig. 2, *C-F* shows the monthly results of treatment with 3 test capsules a day for 1, 2, 3, and 4 months, respectively, and it may be noted that the mean blood loss was markedly reduced from 28.6 pads to 13.7 pads in 4 months of treatment, although only 13 of the 41 women were followed this long. At the same time there was a steady elevation of capillary strength, which usually rose markedly before the menorrhagia was controlled. In Figs. 1, *A*, and 2, *E* and *F* the rise in the mean level of capillary strength appears almost to have ceased in the third and fourth months of treatment, but this may be an artefact since the maximum reading of the petechiometer is 35 cm. Hg and many of the women had already reached this level.

In Fig. 3 only the 12 women with menorrhagia having the lowest mean capillary strengths (all averaging less than 20 cm. Hg before treatment) are considered, with a view to comparing their pattern with the normal. It may be noted that they showed a more irregular pattern and that the normal postovulatory and premenstrual depressions of capillary strength were not evident before treatment. However, treatment resulted in a marked elevation of capillary strength and the return of a distinct premenstrual drop. This absence of the normal pattern, associated with low capillary strength, is evident in many of the individual charts and may be

real or it, too, may be an artefact. One wonders whether the protection afforded the capillaries of the arm by the overlying skin may not in some instances prevent the detection of very low values. Space does not allow the presentation of the records and the individual capillary strength charts of all the patients in this series, but five fairly typical case histories are given below, and the results of treatment of these patients are illustrated in Figs. 4, 5, *A-C,* and 6.

Case reports

Case 1. The patient in Fig. 4, aged 33, para ii, gave a history of heavy, painful menstrual periods and premenstrual spotting for 6 years since the birth of her second child. Her menstrual cycle was usually fairly regular, with a 4 to 5 day loss every 26 days, but there had been occasions when the cycle was as short as 24 days or as long as 30. Her chief complaint was of a very heavy flow on the second day of menstruation, when she would have to change pads every hour. She also complained of frequent epistaxis and of bruising easily. Her dietary history was normal and investigation, including curettage and culdoscopy, had revealed no abnormality. Her basal body temperature chart was suggestive of ovulation.

Treatment with test capsules, as shown in Fig. 4, had no effect on the first menstrual period, which started 5 days after treatment was begun (20 pads), or on the second period (16 pads), but caused a marked improvement in the third period, 2 months after treatment was started (11 pads). The patient had two more normal periods while on continued treatment (12 and 12 pads), but substitution of control capsules resulted in a return of the menorrhagia (19 pads) after 1 month. Treatment with test capsules was therefore resumed and subsequent periods slowly improved again until, 3 months after resumption of treatment, she required only 9 pads per period. The frequency of epistaxis was also markedly reduced, but the premenstrual spotting did not change. Fig. 4 clearly illustrates the fall of the capillary strength on control capsules and the subsequent rise upon returning to test capsules.

Case 2. The patient in Fig. 5, *A,* aged 34, para iv, gave a history of regular menorrhagia since the menarche, and she had occasionally noted spontaneous petechiae. After delivery of her first child, she developed spontaneous hemorrhages on the face. Her last baby had been delivered by cesarean section for placenta previa, and, some days later, after returning home, she developed spontaneous ecchymoses on the legs. She had been investigated 2 years previously and the bleeding time, clotting time, and platelet counts were found to be normal. The menorrhagia returned after the birth of her last child, and during a month of observation without treatment she saturated 21 pads. During 2 months of treatment with control capsules, she had persistent menorrhagia, with blood losses saturating 23 and 22 pads. She ovulated regularly, as evidenced by her basal body temperature chart (Fig. 5, *A*). During the 3 months without test capsules, the capillary strength was low and fluctuating, averaging 20.9, 23.6, and 17.1 cm. Hg. Treatment with test capsules was then started, and subsequent menstrual flows for 4 months were 13, 13, 18, and 13 pads, respectively. The capillary strength response was not as rapid as was the improvement in the menorrhagia, but it did eventually rise, the mean values being 24.2, 23.7, 30.7, and 28.2 cm. Hg during the 4 months of treatment.

Case 3. The patient in Fig. 5, *B,* aged 39, para i, gave a history of regular, heavy, prolonged menstrual periods and tiredness for 1 year. Her cycle had changed from 4 to 5 days every 28 days to 8 to 11 days every 30, and she had developed midcycle spotting as well. Investigation had shown no abnormality to account for this. The menstrual flow was collected in an intravaginal cup and its volume was carefully measured. During 1 month without treatment and 2 months on control capsules, she lost 475, 475, and 482 c.c. of blood, but this was reduced to 227 and 160 c.c. during the 2 months of treatment with test capsules. Also, the intermenstrual bleeding ceased. The capillary strength averaged 21.9, 29.3, and 24.4 cm. Hg without treatment and 30.5 and 32.8 cm. Hg during the 2 months of treatment. The basal body temperature chart was not kept well, and it is not known whether or not she was ovulating.

Case 4. The patient in Fig. 5, *C,* aged 36 para iv, gave a history of using 20 pads per period for most of her menstrual life and complained that this had increased to 36 to 48 pads per period for the past 18 months. Examination revealed a slightly enlarged uterus and first-degree uterovaginal prolapse. Curettage produced normal secretory endometrium and the ensuing menstru-

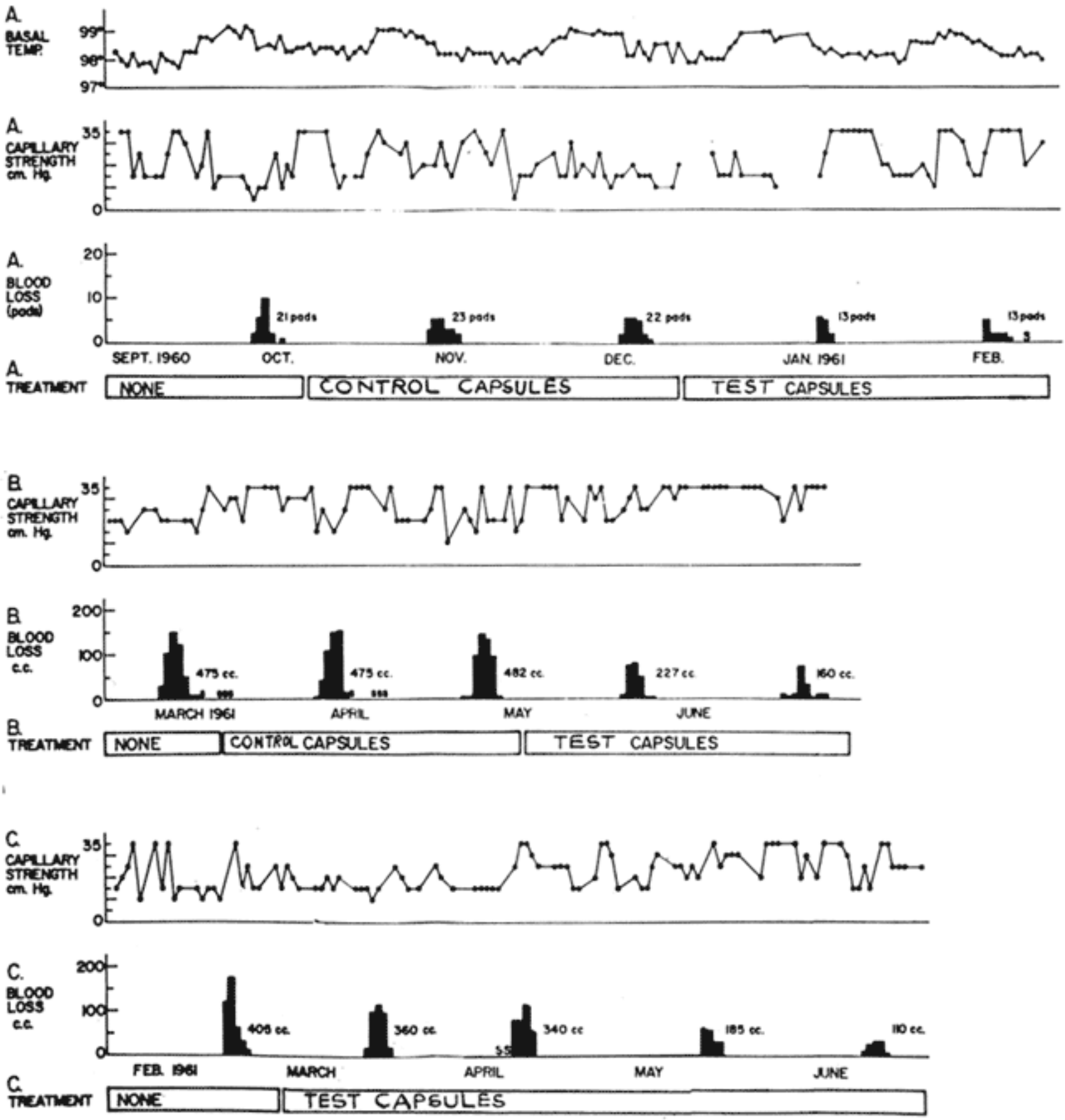

Fig. 5. *A,* Blood loss, capillary strength, and basal body temperature of patient with menorrhagia, before and during treatment with test capsules. Blood loss was reduced from 22 to 13 pads per period as a result of 1 month of treatment. *B,* Blood loss and capillary strength of patient with menorrhagia, showing excellent response to treatment with test capsules. Blood loss, as measured in an intravaginal cup, was reduced from 482 to 160 c.c. in 2 months. *C,* Blood loss and capillary strength record of patient whose blood loss was reduced from 405 to 110 c.c. as a result of 4 months of treatment with test capsules. The simultaneous improvement in capillary strength is quite evident.

ation required only 20 pads. She was then instructed in the use of the intravaginal cup and measured a 405 c.c. blood loss at the next menstruation without treatment. She started taking 1 test capsule three times a day and blood loss in subsequent months of continued treatment was 360, 340, 185, and 110 c.c. The mean monthly capillary strength was 19.3 without treatment and 17.1, 22, 30, and 27.5 cm. Hg during 4 months of treatment.

Case 5. The patient in Fig. 6, aged 31, para iii, had a regular cycle of 5 to 6 days every 25 to 28 days, but she had been troubled by heavy menstrual periods ever since the menarche at

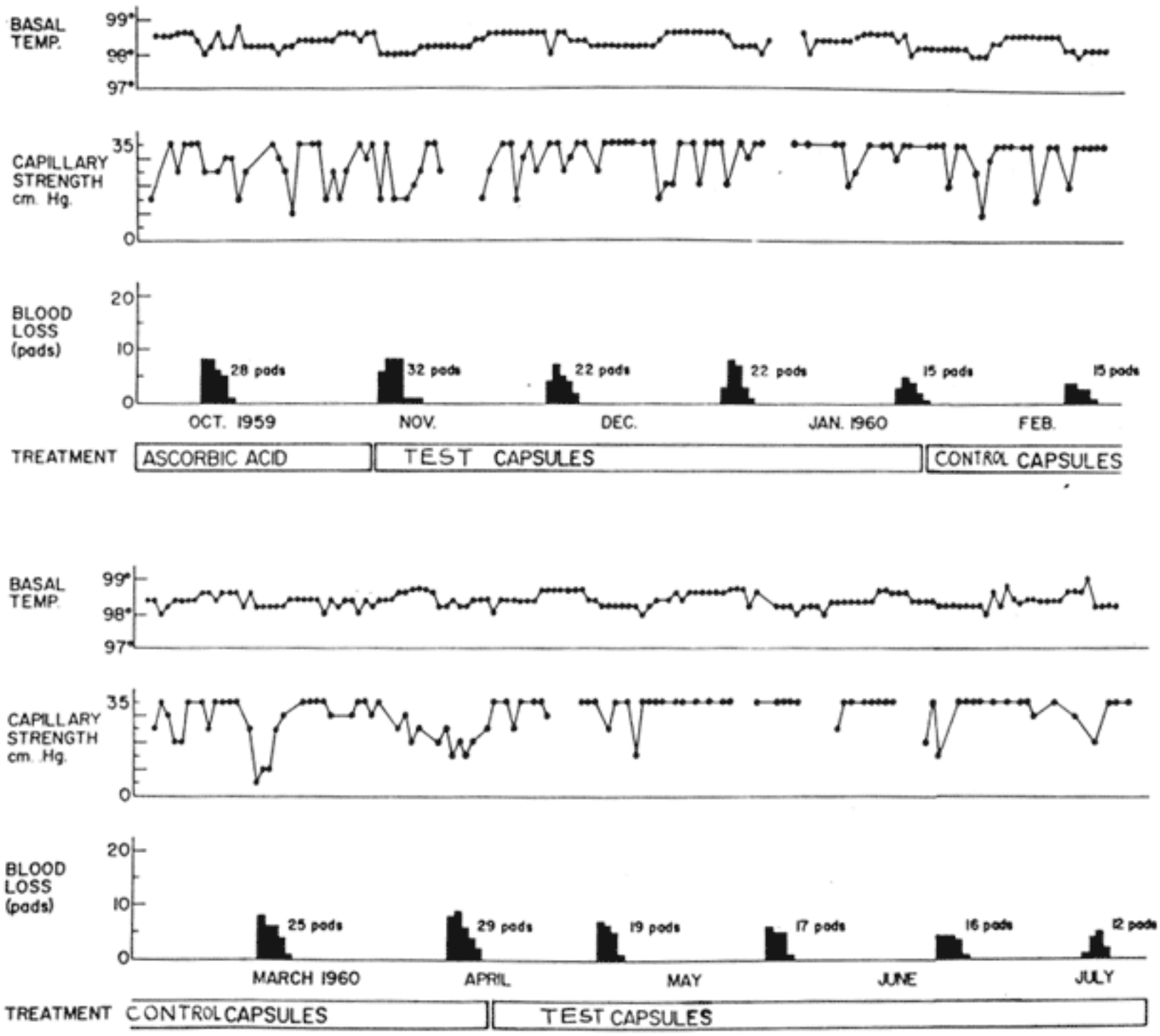

Fig. 6. Basal body temperature, capillary strength, and blood loss of a patient as described in the text. This patient had been using 36 to 48 pads per period, but this loss had been reduced to 28 pads as a result of 6 months of treatment with ascorbic acid, 100 mg. daily. Treatment with test capsules caused further reduction of blood loss to 15 pads per period. Menorrhagia returned and blood loss rose again to 29 pads per period as a result of 3 months on blank capsules, but renewed treatment with test capsules reduced blood loss again and she required only 12 pads per period after a further 4 months of treatment.

13 years of age. She had been using as many as 48 pads per period, but this number had been reduced to 28 pads per period after she took ascorbic acid, 100 mg. a day continuously for 6 months. She was still taking ascorbic acid during the initial month of study before she began taking the test capsules. Nevertheless, during 4 menstrual periods during treatment with test capsules the flow was further reduced, and she used 32, 22, 22, and 15 pads, respectively. When control capsules were substituted, the heavy blood losses returned after a month and she used 15, 25, and 29 pads during the next 3 cycles. Renewal of treatment with the test capsules in the same dosage again controlled the menorrhagia, with losses reduced to 19, 17, 16, and 12 pads in the next 4 months. The basal body temperature chart showed definite evidence of regular ovulation. The capillary strength pattern was relatively normal even before treatment, but the monthly mean capillary strength level rose from 25.9 to 30, 30.5, and 32.4 cm. Hg during treatment, fell to 30, 27, and 27.8 cm. Hg on control capsules, and rose again to 33.2, 34.2, 32.8, and 32.2 during resumed treatment. The patient's dietary history revealed that she had been getting about 100 mg. of vitamin C daily in her diet, in addition to the daily

supplement of 100 mg. which she had received for 6 months. If one assumes that 200 mg. a day is an adequate intake of vitamin C, then one must assume that the water-soluble citrus bioflavonoids were entirely responsible for the further improvement while taking the test capsules. However, it is conceivable that this patient may have had a defect in the absorption or utilization of vitamin C and that the increase of her supplement from 100 mg. to 600 mg. of ascorbic acid a day may have been a significant factor in the clinical improvement.

Comment

There is no doubt that treatment with water-soluble citrus bioflavonoids and ascorbic acid markedly reduced the blood loss of the majority of patients with menorrhagia in this series, but this therapy was very slow to act and 2, 3, or even 4 months of treatment were sometimes required before full benefit was obtained.

The 2 patients who had menorrhagia associated with cystic hyperplasia of the endometrium did not respond to this treatment, and one gains the impression that only ovulatory menorrhagia responds. Most of the women with menorrhagia were found to have low capillary strengths which rose considerably during treatment and remained elevated for a month or so after treatment had been discontinued. This improvement of capillary strength resulting from bioflavonoids and vitamin C therapy suggests a dietary deficiency, and, indeed, dietary histories disclosed that many of these women had been on a diet deficient in fresh fruit. There were, however, several instances of a similar improvement of capillary strength in women whose fruit intake had apparently been adequate, and this suggests that a failure of absorption or an increased requirement for bioflavonoids may have been the basis of their disorder. Indeed, even with the test concentrate, the response was so slow in some patients as to suggest an impairment of absorption or utilization.

Women with a recent onset of menorrhagia seemed to respond more quickly than did those with a long history of this disorder. Many of the best results were obtained in women with menopausal menorrhagia, and yet 2 of the most dramatic responses were in young girls, aged 13 and 17 (not included in this series), who had been bleeding on and off almost continually for 1 year and 18 months, respectively, in spite of various forms of treatment. The abnormal bleeding of both of these girls ceased within 1 week after treatment was started, and they developed normal menstrual cycles.

Although most of the patients with regular ovulatory menorrhagia in this series had low capillary strengths which improved with treatment, there were some, especially those with obese arms, whose capillary strengths seemed to be normal before treatment, yet whose menorrhagia improved considerably as a result of treatment. In such cases one wonders about the adequacy of the test.

After completion of our studies and after 3 or 4 months of treatment with the concentrate, we gave the patients dietary advice and attempted to find out whether the benefits of treatment could be maintained by their eating citrus fruit and tomatoes. It was explained that the juice from an orange contains abundant vitamin C, but has only one tenth of the bioflavonoid (vitamin P) content of the fruit itself, as the bioflavonoids are found mainly in the pulp and peel. The need for eating the flesh of the citrus fruits rather than drinking the juice was stressed. Often the consumption of 3 oranges or 3 tomatoes a day was sufficient to maintain normal menstruation, but in women who had had menorrhagia for many years, it usually became necessary to revert to the bioflavonoid-vitamin concentrate.

Three of the women in this series became pregnant during treatment with the concentrate, and one of them had previously been infertile, which demonstrates that the compound does not suppress ovulation. Prueter[5] has found similar benefits from the use of this product in the treatment of dysfunctional uterine bleeding, and 6 of his patients (3 previously infertile) became pregnant during treatment. Therefore, this may even represent a new treatment for infertility associated with menorrhagia. One of the

more notable features of this study was the marked sense of well-being many of the patients experienced after treatment with the test capsules. Substitution of the control capsules usually resulted in a fall of capillary strength, and the women again did not feel well, with various aches and pains, headaches, and depression. Many of these complaints ceased when the capillary strength rose as a result of renewed treatment.

Chemical nature of the bioflavonoids. The true composition of the citrus bioflavonoid mixture used in this study is unknown. Apparently it contains 75 per cent of flavonoid glycosides and polyphenolic compounds, but Menkin[6] states that hesperedin, the original citrin or vitamin P of Szent-Györgyi, is not present since it is eliminated in the preparation of the mixture.

There is a wide variety of plant flavonoid substances, including flavones, flavonols, and flavonones and their derivatives. It is particularly interesting that some of the naturally occurring isoflavones, such as daidzein, genistein, and biochanin A, are weak proestrogens,[7] possessing one-fifty thousandth the estrogenic potency of stilbestrol. Moreover, genistein has been known to cause cystic hyperplasia of the endometrium in sheep grazing on subterranean clover in Australia.[8-10] The chemical formulas of these substances are shown in Fig. 7, along with those of the synthetic estrogen, diethystilbestrol, and the natural ovarian estrogen, estradiol, so as to show the distal separation of their acidic hydroxyl groups, comparable to positions 3 and 17 of the steroid nucleus.

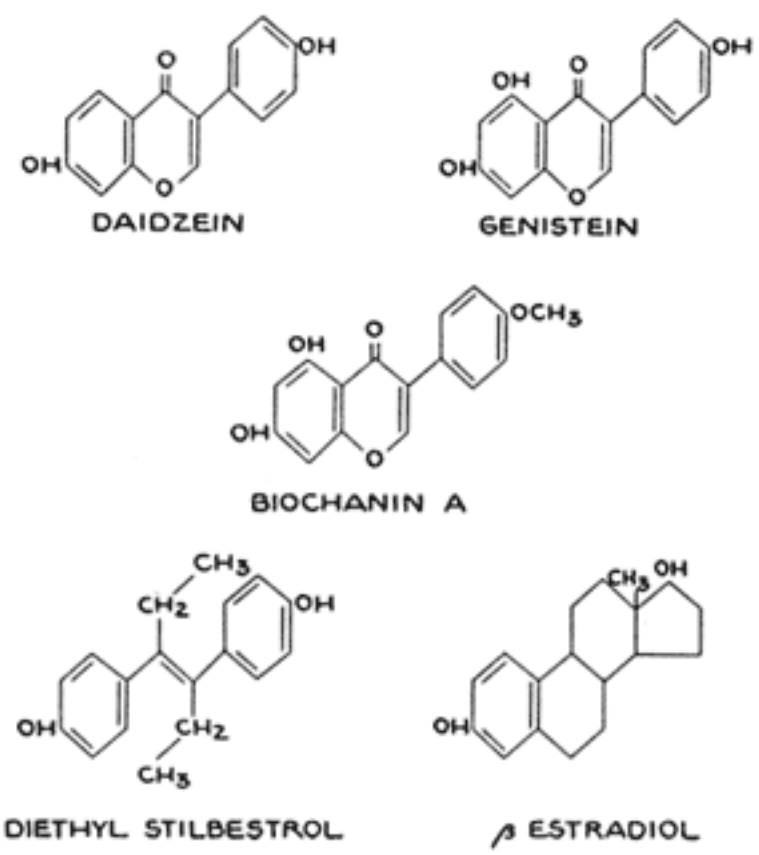

Fig. 7.

Biochanin A has a methoxy instead of a hydroxyl group at a position equivalent to 17, and this methyl ester seems to be about equally effective. Other flavonone and flavonol glycosides, such as hesperedin and rutin, believed to possess capillary fortifying action but not known to be estrogenic, have aglycones which differ from the estrogenic isoflavones mainly in the positions of their acidic hydroxyl groups.

In Fig. 8 rutin and hesperedin have been rotated so as to show free or esterified acidic hydroxyl groups in positions equivalent to 3 and 4, but none equivalent to position

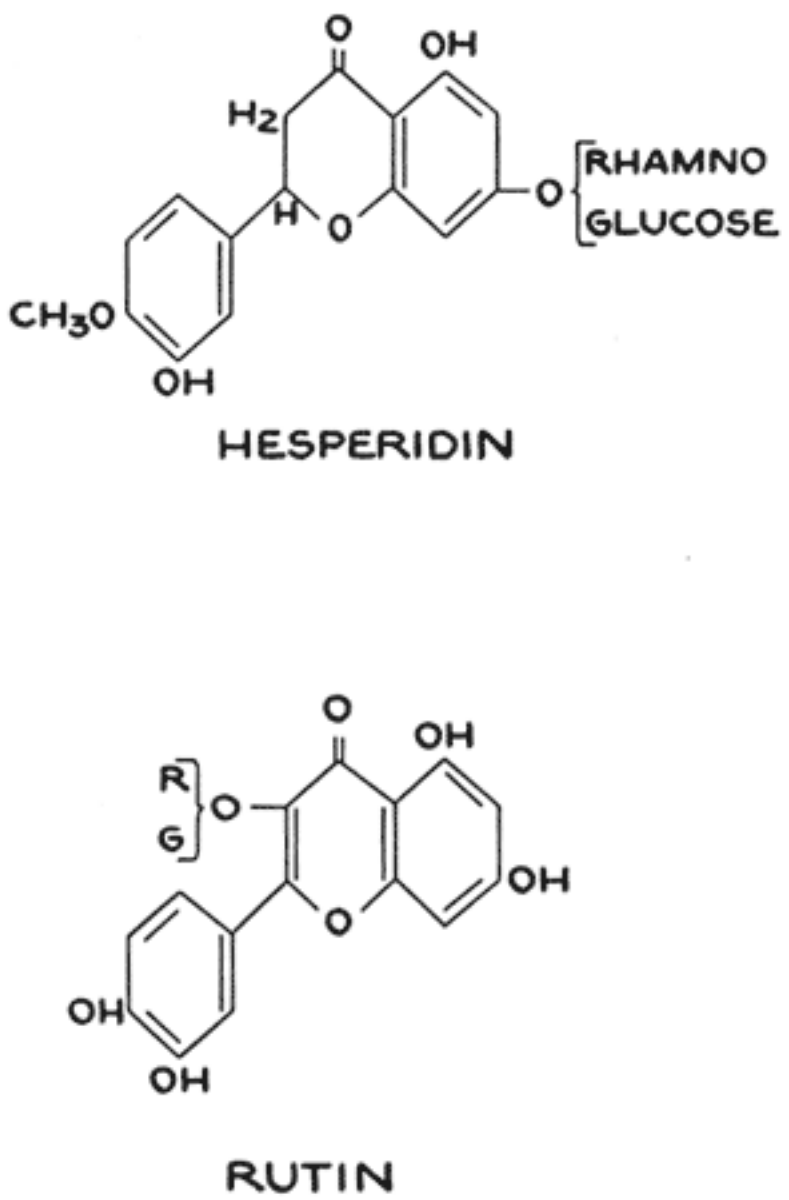

Fig. 8.

17. It seems that the spacial separation of an acidic hydroxyl group in position 3 and another hydroxyl in a position equivalent to 17 results in estrogenic activity, whereas acidic hydroxyl groups in certain other positions result in capillary fortifying action without estrogenic activity. It is conceivable that the natural estrogens enter into competition with the bioflavonoids for a substrate, probably the mucopolysaccharides, in the capillary sheath and in the ground substance.

Thus, the estrogens could be envisaged as displacing the bioflavonoids from the capillary sheath but continuing to maintain capillary integrity until they are metabolized or withdrawn, when the capillaries would become weak until such time as the bioflavonoids could return to strengthen them.

Unfortunately we do not know which of the many flavonoid substances is most potent in capillary fortification, and for this reason any speculations must remain entirely hypothetical.

Conclusions

Regular ovulatory menorrhagia is commonly associated with a capillary weakness which may be detected by the use of a suction petechiometer applied to the skin of the inner aspect of the upper arm. One test is of little value, however, and daily testing for a whole month is needed for an adequate study.

Oral treatment with water-soluble citrus bioflavonoids and ascorbic acid causes a marked reduction in the blood loss of most women with regular ovulatory menorrhagia. This therapy is slow to act and 2, 3, or even 4 months of continual treatment may be required to achieve maximum benefit. Nevertheless, this is a genuine response to treatment because menorrhagia has been shown to return in 4 to 6 weeks if control capsules are substituted and to improve again with renewed treatment.

There is a definite elevation of capillary strength associated with the reduction of menstrual blood loss, and, moreover, the patients experience considerable improvement in their sense of well-being.

This form of treatment can be used for all women with menorrhagia who do not improve after a diagnostic curettage, irrespective of their capillary strengths. It does not seem to help patients with cystic hyperplasia of the endometrium, but it is effective in the presence of small uterine myomas. There are apparently no contraindications to this therapy.

The water-soluble citrus bioflavonoid compound with ascorbic acid (duo-C.V.P.) and the control capsules were supplied by the courtesy of Dr. Harvey S. Sadow and Mr. R. H. Wygant of the Arlington-Funk Laboratories Division of the U. S. Vitamin and Pharmaceutical Corporation, Montreal, Quebec, and New York, New York. The Tassette cups were provided by the Tassette Company of Stamford, Connecticut.

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