

# CAPILLARY STRENGTH AND THE MENSTRUAL CYCLE\*

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## *Introduction*

Although a great deal of work has been done on the natural mechanisms for the arrest of bleeding, such as platelet plugging, fibrin formation, and arteriolar spasm, relatively little work has been done on the factors initiating hemorrhage.

Trauma is undoubtedly the commonest cause of vascular damage, but the degree of trauma required to rupture an arteriole, capillary, or venule, varies from person to person and from time to time; it also depends on the season of the year and the part of the body affected. The uterus is particularly interesting in that it is a well-protected organ that bleeds without any obvious physical trauma.

Detailed studies of the endometrium by Markee (1940), Bartelmez (1957), and many others have familiarized us with the histological changes that take place in the uterus during ovulatory and nonovulatory menstrual cycles, and we know that these changes result from fluctuations in the ovarian hormone levels but, in spite of many theories, the actual cause of menstrual bleeding remains obscure.

Markee has often been misquoted as stating that menstruation in the rhesus monkey results from spasm of the spiral arterioles. In fact Markee stated: "It, therefore, seems reasonable to conclude that regression of the endometrium and the consequent compression of the coiled artery, decreases the blood supply to the functional zone sufficiently to cause injury to it, and that the actual contraction of the deeper portion of the coiled artery occurs as the result of the elaboration of some substance by the degenerating endometrium. If this is true, vasoconstriction should be regarded not as a cause of menstruation, but as a defense mechanism which prevents an excessive loss of blood from injured vessels. A further reason for doubting that vasoconstriction causes the bleeding is the fact that the imminence of menstruation is indicated by other phenomena one to five days before vasoconstriction begins."

Reynolds (1949) states that several species of New World monkeys (*Cebus*, *Ateles geoffroyi*, and *Alouatta palliata*) menstruate without spiral arterioles; furthermore in women menstrual bleeding regularly occurs in deposits of endometriosis where spiral arterioles are usually absent; therefore, clearly, coiling of the arteries is not essential to the process.

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Bartelmez lays stress on the loss of ground substance from the endometrial stroma before menstruation, and it has been shown by Schiff (1959), studying nasopharyngeal angiofibromata, that the stroma of this tumor is profoundly influenced by estrogens. The work of Zachariae (1959) suggests that acid mucopolysaccharides, such as hyaluronic acid in the endometrial stroma (also found in Wharton's jelly and in the sexual skin of the baboon) are produced and polymerized under estrogenic stimulation and depolymerized or destroyed by estrogen lack.

While the factors responsible for capillary integrity are incompletely known, there is evidence (Zweifach, 1955) that "the most common forms of increased capillary fragility are a consequence of a disturbance in the capillary sheath. The perivascular sheath undergoes changes in its physicochemical characteristics, in addition to those in the tissue-ground substance, and is profoundly altered by enzymes with hyaluronidase activity. In vitamin C-deficiency states in the guinea pig, this structure is likewise found to be deficient."

Variations in capillary strength with menstruation have been shown by Stephan (1921), Brewer (1938), Salvatore (1952), and Van der Burg (1953), but their work did not receive the attention it deserved. Brewer, using the skin-suction test, found a regular premenstrual drop in capillary strength, as shown in FIGURE 1 taken from his work. However, a decreased capillary strength at mid-cycle was only occasionally evident in Brewer's charts and was not shown in Van der Burg's because he did not test his subjects frequently enough.

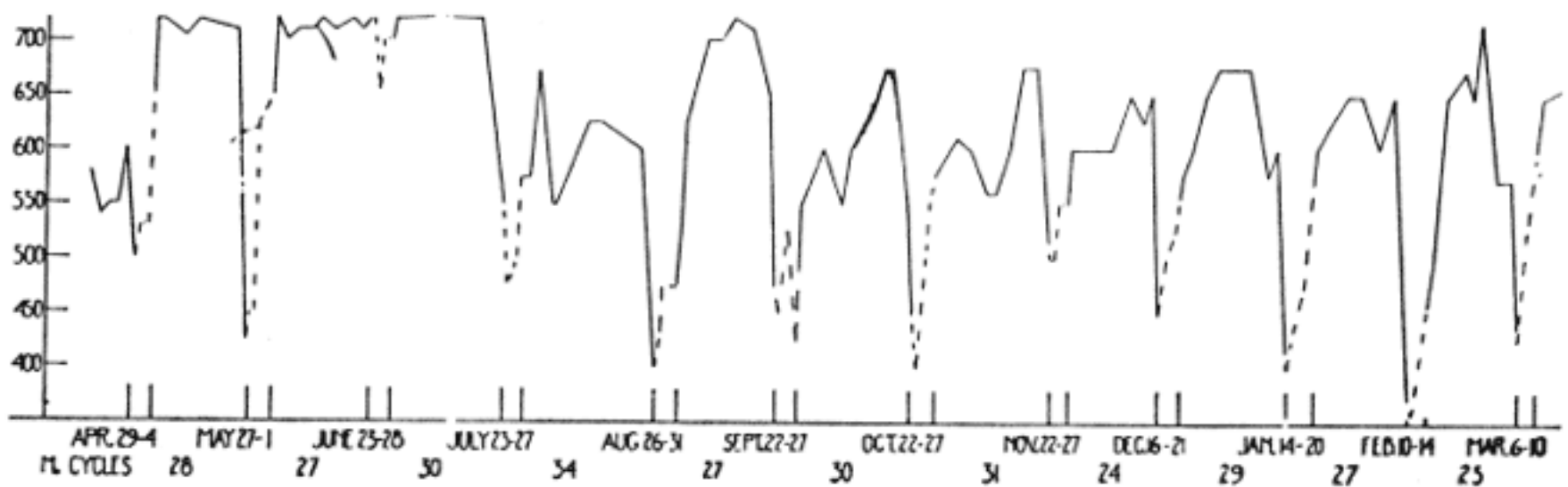


FIGURE 1. This illustration shows a regular premenstrual drop and an occasional postovulatory drop in capillary strength. Reproduced from Brewer by permission of the *American Journal of Obstetrics and Gynecology*.

FIGURE 2, also from Brewer's work, clearly shows the seasonal variation in capillary strength, which has been well established by many workers in several fields. This patient of Brewer is particularly interesting in that she developed menorrhagia during the period of decreased capillary strength.

Salvatore, using a venous congestion method, simply compared men-

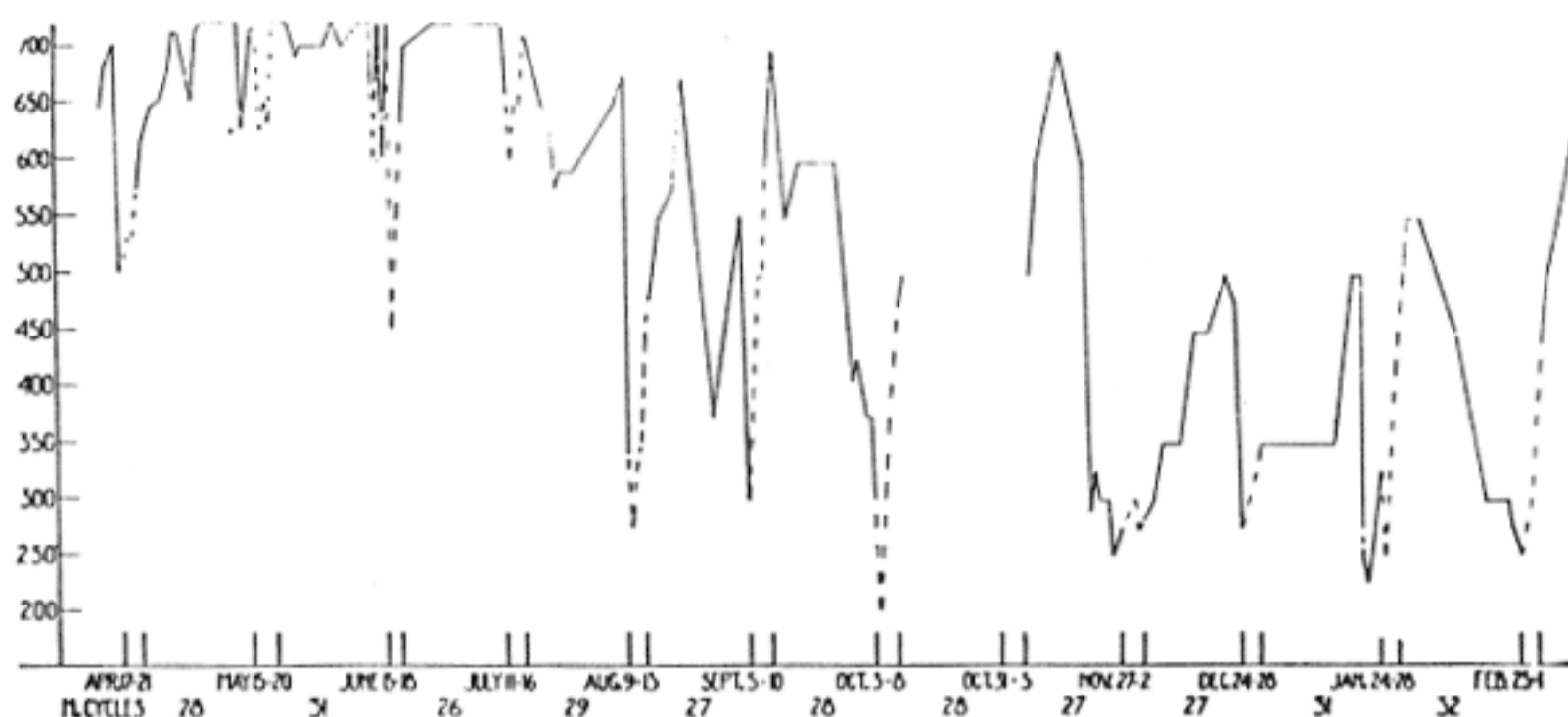


FIGURE 2. Seasonal variations in capillary strength. This patient developed menorrhagia in August. Reproduced from Brewer by permission of the *American Journal of Obstetrics and Gynecology*.

strual and intermenstrual values as two groups and did not carry out daily tests.

It is now fairly well established that both vitamin C and the bioflavonoids are essential in the diet for the maintenance of the integrity of the capillary wall and that, without either of them, bleeding can easily occur (Bentsath *et al.*, 1936; Martin, 1955; and Robson and Duthie, 1950).

The works of Robson and Duthie (1950), Kramar (1954), Shulman *et al.* (1955), and McMurray and Jaques (1959) have demonstrated that mild stress or cortisone raises capillary strength while DOCA, and salt or severe stress have the opposite effect.

Capillary strength is decreased in many infectious diseases such as scarlet fever, measles, and influenza, and there is evidence to suggest that fragility of the capillaries may predispose to rheumatic fever and several other diseases (Ainslie, 1959; Boines, 1955; Greenblatt, 1955; Jacobs, 1956; Javert, 1955; and Rinehart, 1955).

Thus in any study of capillary strength, one must consider species, diet, drugs, season, temperature, health, stress, hormonal state, and the part of the body to be tested.

#### Method

Many tests for capillary strength or fragility have been devised, but only the positive pressure-cuff tests, relying on venous congestion, and the suction tests seem to give reliable results.

In earlier works the term "capillary fragility" was used but, as the normal state represents a negative fragility, the term "capillary resistance" was coined to give positive values. However, this term might

suggest a resistance to the flow of blood through the capillaries that is not intended; consequently the term "capillary strength" seems preferable and is used in this article.

It is known that spontaneous hemorrhage may occur from arterioles and venules as well as capillaries, as was observed by Markee (1940) in endometrial tissue implanted in the eyes of rhesus monkeys. Perhaps "small blood vessel strength" would therefore be a more accurate term, as one is not sure that the petechiae produced by suction always represent capillary hemorrhage. However, capillary strength is less cumbersome: it has the advantage that it can be represented as a positive gain, and it does not connote any interference with blood flow, moreover this term remains quite distinct from capillary permeability.

In this investigation we have relied entirely upon the skin suction test and have used the simple instrument known as the petechiometer.\* This simple and convenient instrument has been tested by Brown (1949) against a modified Dalldorf resistometer: only 10 per cent of the patients showed readings by the two instruments that differed by more than 5 cm. Hg. The petechiometer consists basically on a cylinder containing a piston on a spring; the piston is marked off at 3 points by grooves representing 10, 20, and 30 cm. of Hg suction. The cylinder is connected to a transparent-plastic bell 2 cm. in diameter and contains a magnifying lens for inspection of the skin. All tests were carried out on the skin of the medial aspect of the upper arm, and suction was exerted at a given pressure for exactly 1 min. Thirty sec. after removing the petechiometer a search was made for petechiae with a bright light. If no petechiae were found the test was repeated using a greater suction. A liberal amount of surgical lubricant was smeared on the area of skin to be tested in order to ensure a good seal. The medial aspect of the upper arm was chosen because it was an accessible area that developed petechiae at lower negative pressures than the antecubital fossa.

If 1 or 2 petechiae were produced by suction at 30 cm. Hg, then 30 cm. Hg was recorded as the capillary strength. However, if many petechiae were produced at 30 cm. Hg, and there were none at 20 cm. Hg, then the result was recorded as 25 cm. Hg. Thus with this instrument one can have results recordable as 0, 5, 10, 15, 20, 25, 30, and 35 cm. Hg. The 35 cm. Hg is recorded when no petechiae are produced by suction at 30 cm. Hg, although clearly this result could represent any higher figure.

Tests have been carried out almost every day on 33 normal nurses during 42 menstrual cycles, and on many patients. In all, more than 5000 tests have been made on human subjects, but this paper is principally concerned with the normal menstrual cycle.

\*Obtained from Bentlich Inc., Chicago, Ill.

Observations of the menstrual flow have been made by counting the number of pads saturated and, in some instances vaginal tampons have been used throughout the cycle to observe any slight bleeding that may occur at mid-cycle. Other investigations have included daily blood pressure, pulse rate, rectal temperature, body weight, and skinfold thickness measurements; on some subjects platelet counts and platelet stickiness estimations have been performed, but only the rectal temperatures, the platelet counts, and the capillary strength estimations seemed to show any definite relationship to the menstrual cycle.

### *Results*

The changes in capillary strength during the menstrual cycle of a healthy fertile married woman (aged 24) with 1 child (subject No. 20), who has a fairly regular 24 to 26 day menstrual cycle are shown in FIGURES 3 and 4.

FIGURE 3 shows the results of twice-daily tests of capillary strength along with other observations made during the same menstrual cycle; it may be observed that the changes in capillary strength are even more striking than the changes in basal body temperature. The mid-cycle platelet peak described by Pepper and Lindsay (1959) is plainly evident in FIGURE 3, but it appears to have occurred after ovulation.

FIGURE 4 shows consecutive daily observations on the same subject for 9 mo., and clearly illustrates the regular premenstrual drop in capillary strength present in nearly all the subjects tested. Sometimes the premenstrual drop continued during the first few days of menstruation, but usually the capillary strength began to return to normal on the first day of the flow. This subject (No. 20) was particularly useful because she experienced "mittelschmerz" pain fairly regularly at the time of ovulation, nearly every month, either once or occasionally twice. Close inspection of FIGURE 4 shows that a sharp drop in the capillary strength occurred consistently 2 days after the pain on every occasion; moreover this "postovulatory" drop occurred twice in August when she experienced the pain twice; in retrospect there is also evidence of double ovulation in June and July, although she experienced pain only with the first ovulation in June and with the second ovulation in July. No pain was experienced in October, but the vaginal tampon technique had then been instituted, and very slight bleeding was thus detected on the 12th day: a definite postovulatory drop in capillary strength occurred 3 days later on the 15th day of the cycle. One had supposed that this mid-cycle or postovulatory drop in capillary strength might be the cause of the mid-cycle bleeding that sometimes occurs in women, and that this might be analagous to the bleeding that occurs at estrus in many other mammals.

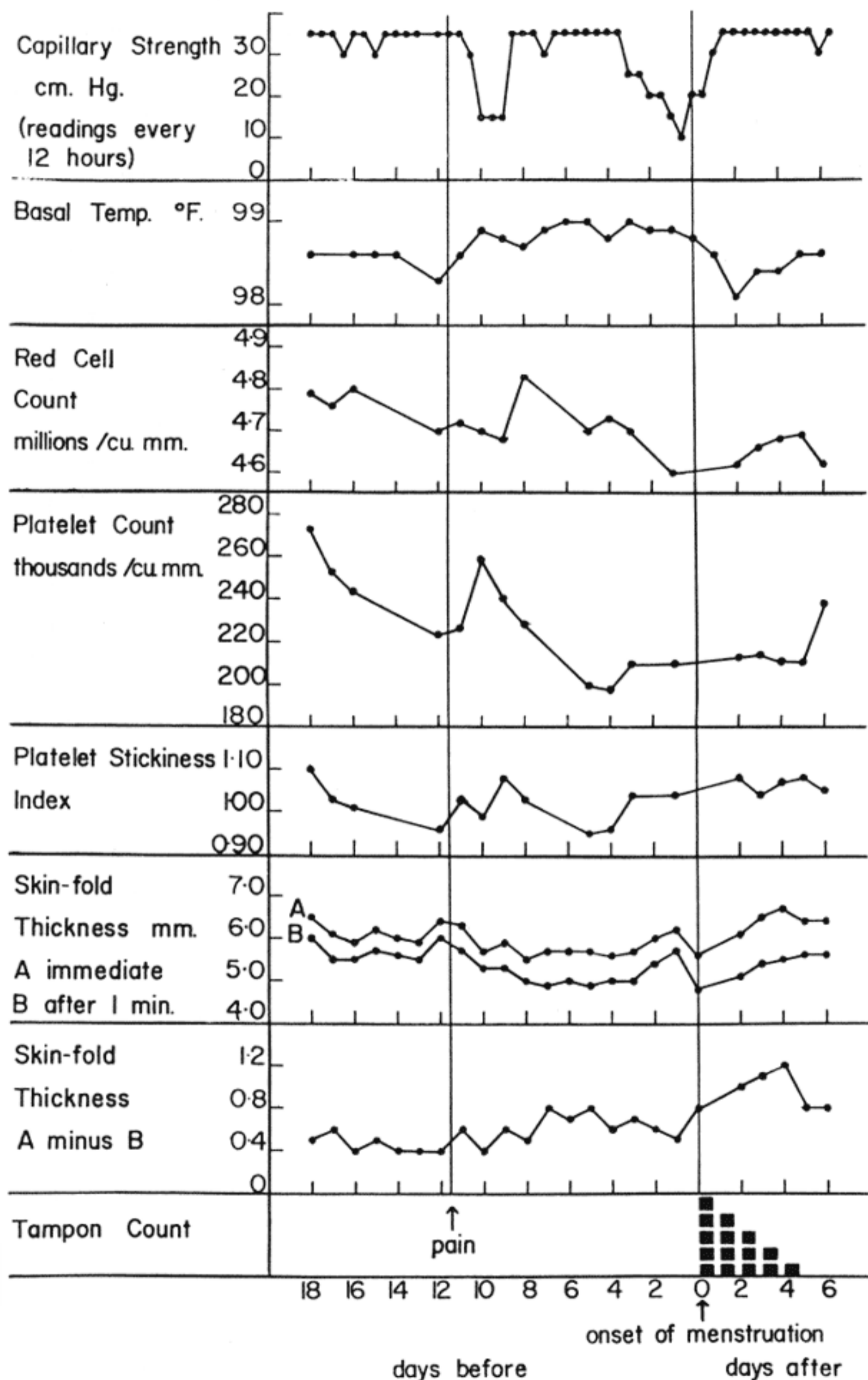


FIGURE 3. The graph shows the changes in capillary strength and other observations during the same menstrual cycle of a normal woman (No. 20).

It was therefore surprising to find that the tiny spot of bleeding in October occurred 3 days before the drop in capillary strength and could not therefore have been due to it. However by analogy with the timing of

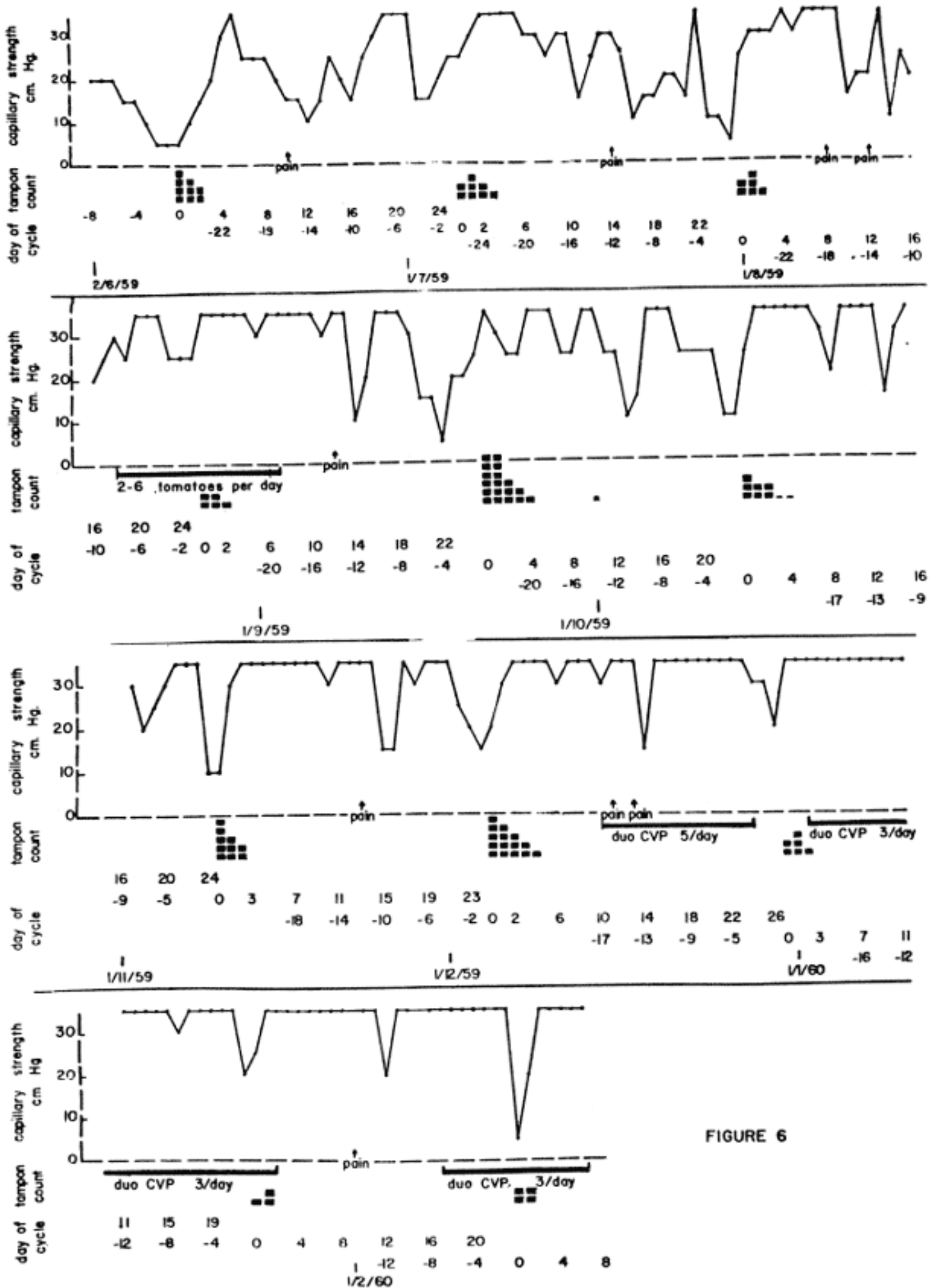


FIGURE 6

FIGURE 4. Daily capillary-strength estimations for 9 mo. on a normal fertile married woman (subject No. 20), aged 24, who has a fairly regular 24 to 26 day menstrual cycle (see text).

the pain in other cycles, it now seems almost certain that this slight bleeding arose from the ovary at the time of ovulation, passed along the fallopian tube to reach the uterus, and did not represent uterine hemorrhage. Usually the postovulatory drop in capillary strength is similar in degree to the premenstrual drop, but it does not last as long; moreover it occurs during the platelet peak, which may account for the absence of bleeding at this time. The amount of bleeding was estimated by counting the number of saturated tampons, indicated as black squares in FIGURE 4. In August the tomatoes in this woman's garden became ripe and were consumed by her in large quantities; it may be significant that both the premenstrual drop in capillary strength and the amount of blood lost during the August menstruation were much less than normal.

In December she started taking water-soluble bioflavonoids and vitamin C\* in the high dosage of 5 capsules a day, by mouth, shortly before ovulation. This treatment definitely reduced the amount of the blood loss at the ensuing menstruation, and the premenstrual drop in capillary strength was less than normal, but she experienced colicky premenstrual dysmenorrhea. Treatment was therefore discontinued until after menstruation, when it was reinstated at a lower dosage, using 3 capsules a day. On this regime, during January, there was no evidence of ovulation on her rectal temperature chart, she did not experience the mittelschmerz, and there was no mid-cycle drop in capillary strength; therefore, presumably, ovulation did not occur. However, the blood loss at the next "period" was markedly reduced, and only 3 vaginal tampons were needed. The patient says she cannot remember ever having had such a light period. Bioflavonoids were withheld until after ovulation in February, but the consumption of 3 capsules a day for 7 days before menstruation resulted in another very light period with the use of only 2 tampons a day for 2 days.

Thus the 3 periods, under the influence of water-soluble bioflavonoids and vitamin C saturated a total of 13 tampons, while the previous 3 periods had saturated 32 tampons.

Although it seems that high dosage of bioflavonoids may inhibit ovulation, there is good evidence from our own work and that of others that normal dosage does not inhibit ovulation and may even enhance fertility.

A complete analysis of the results of capillary-strength estimations carried out on 33 nurses during 42 menstrual cycles is shown in FIGURE 5. All these women had normal menstrual histories, and most of them showed evidence of ovulation; unfortunately, however, owing to week ends and days off-duty, some of their charts have gaps that preclude any definite diagnosis.

\*Duo CVP, obtained from Arlington - Funk Laboratories, New York, N. Y.

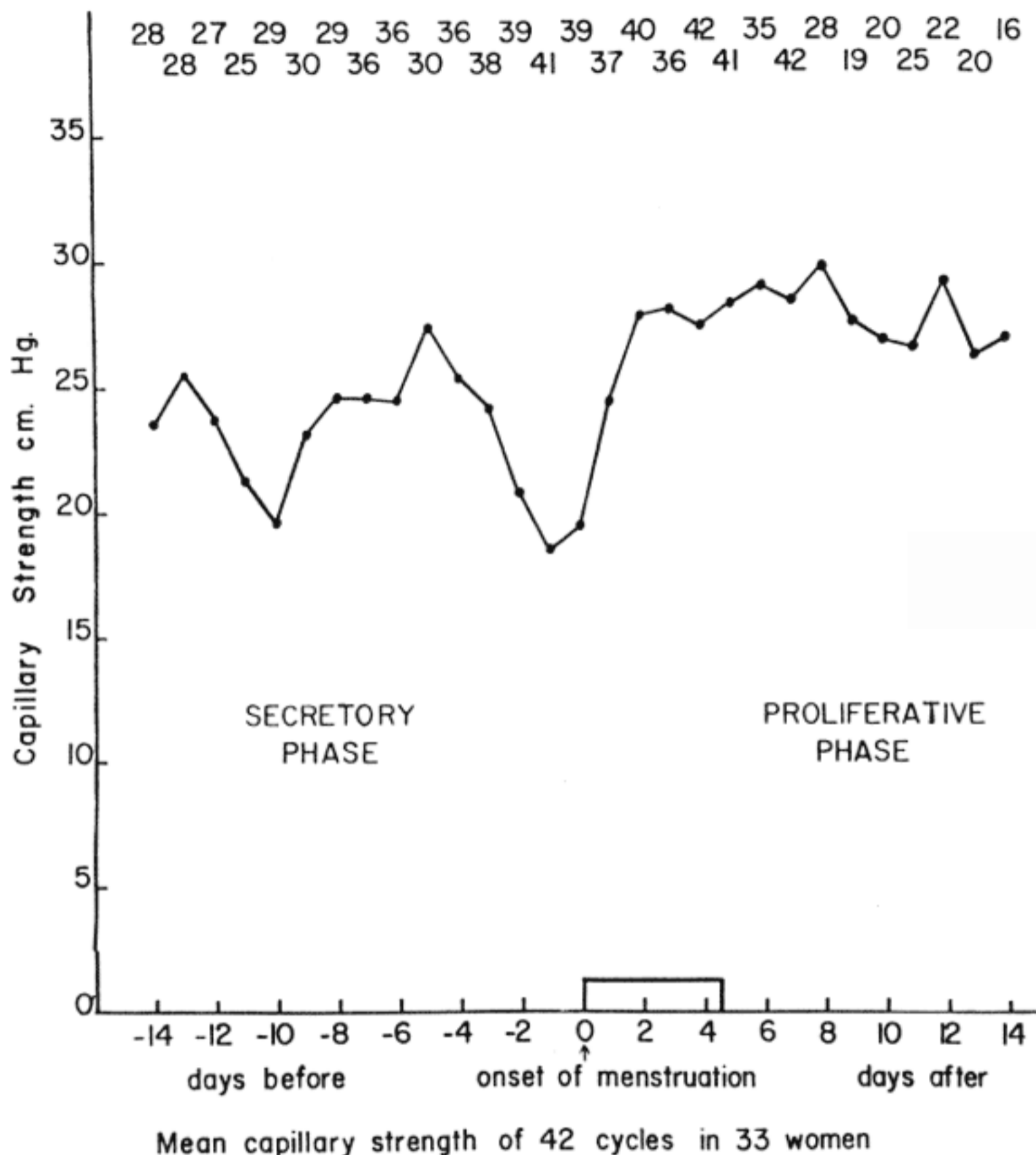


FIGURE 5. Mean results of daily capillary-strength estimations on 33 nurses during 42 incomplete menstrual cycles. The times in the cycle have been calculated as days before or days after the onset of menstruation, and the results for the 42 cycles have been superimposed at day 0 to show the changes in capillary strength at this time. The numbers of estimations from which each daily mean was obtained are shown along the top of the graph.

In FIGURE 5 the days of the cycle are represented as days before and days after the onset of menstruation, and the means of the results obtained on each day, in all 42 cycles, have been superimposed on one another at day 0. In this way it was hoped that a true picture of the average depth and timing of the premenstrual drop would be obtained but, since ovulation occurred in these women a variable number of days before menstruation, the postovulatory drop appears wider and shallower than it really is. Actually the premenstrual drop is also distorted; it is usually deeper and of shorter duration than it appears on this composite graph, as there seems to be some variation in the interval between the drop in

capillary strength and the onset of menstrual bleeding. Moreover the capillary strength occasionally begins to rise again before vaginal bleeding becomes evident; possibly in such instances petechial hemorrhages may have already occurred in the endometrium. The picture may also have been distorted by the inevitable inclusion of at least 1 infertile woman with regular menses, who showed no evidence of ovulation and whose capillary strength chart showed an irregular pattern. However, this composite graph (FIGURE 5) does show both the postovulatory and the premenstrual depressions in capillary strength, and it will serve for comparison with a group of women with menorrhagia. The number of observations from which each daily mean was obtained is shown along the top of the graph.

FIGURE 6 shows a similar graph of the daily mean capillary-strength values of 1 woman (subject No. 20) during 8 menstrual cycles. It is par-

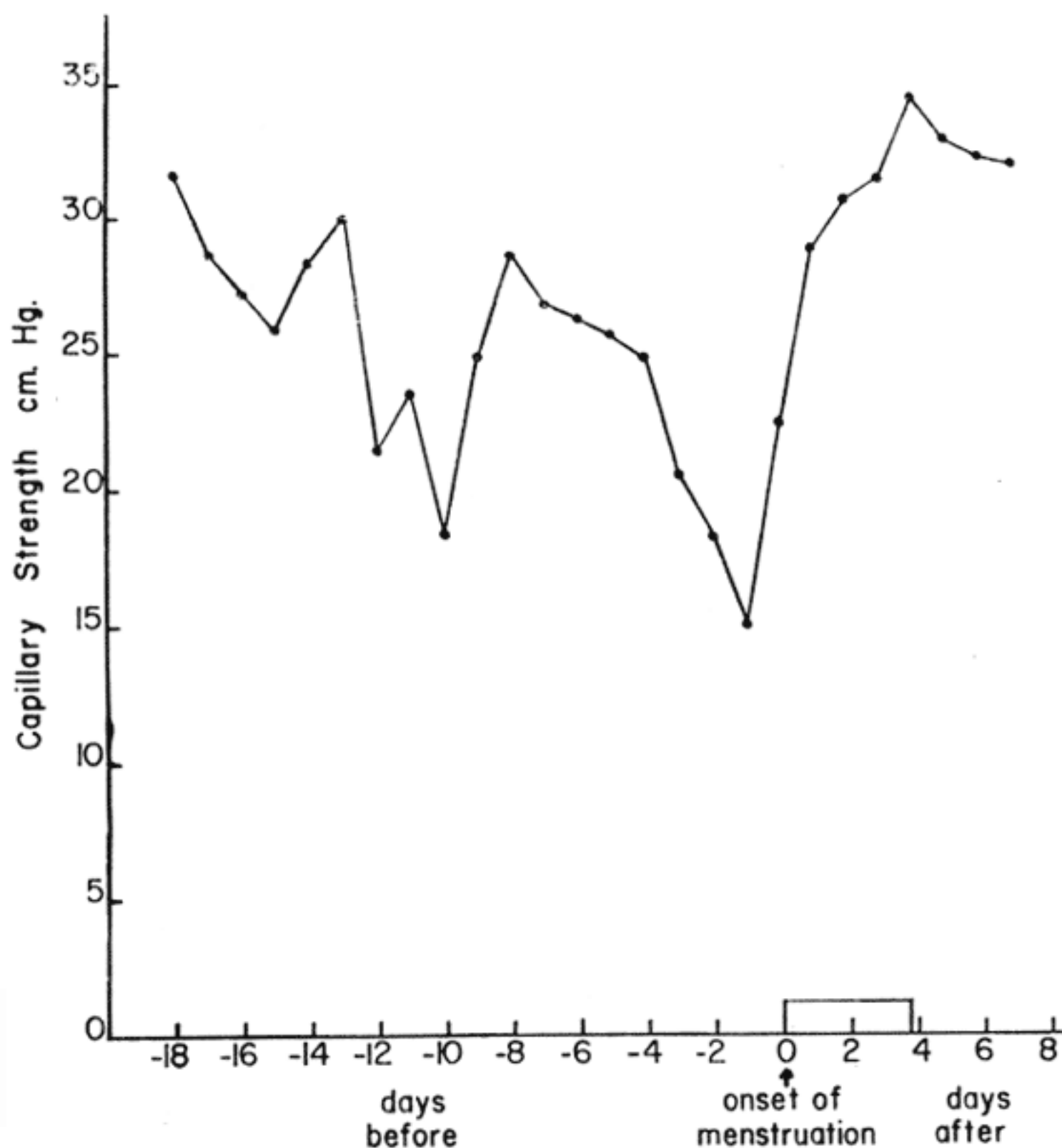


FIGURE 6. The mean daily capillary strength determinations on 1 woman (No. 20) during 8 menstrual cycles of 24 to 26 days. The results are superimposed at day 0, as in FIGURE 5.

ticularly interesting to note that her tendency to double ovulation, evident in some of her monthly charts, is shown again here in the composite graph by a small postovulatory drop on day minus 15, in addition to the main postovulatory drop on day minus 10 or 12.

One woman aged 22 with secondary amenorrhea of 2 years duration was studied; she had an atrophic endometrium and the defect appeared to be in the pituitary, as she was slightly hypothyroid and had subnormal urinary gonadotrophin (FSH) levels; a daily record of her capillary-strength and basal-body temperature during oral hormone treatment is shown in FIGURE 7. She was given ethinyl estradiol 0.05 mg. t.i.d. continuously for 19 days and secrosteron (BDH) an oral progesterone 5 mg. t.i.d. as well, for the last 10 days. Both hormones were withdrawn on the same day and bleeding started 3 days later. It may be noted that the capillary-strength changes closely simulated the premenstrual drop

WOMAN WITH SECONDARY AMENORRHEA OF 2 YEARS DURATION  
AGE 23. THYROID & F.S.H. DEFICIENCY. (no. 22)

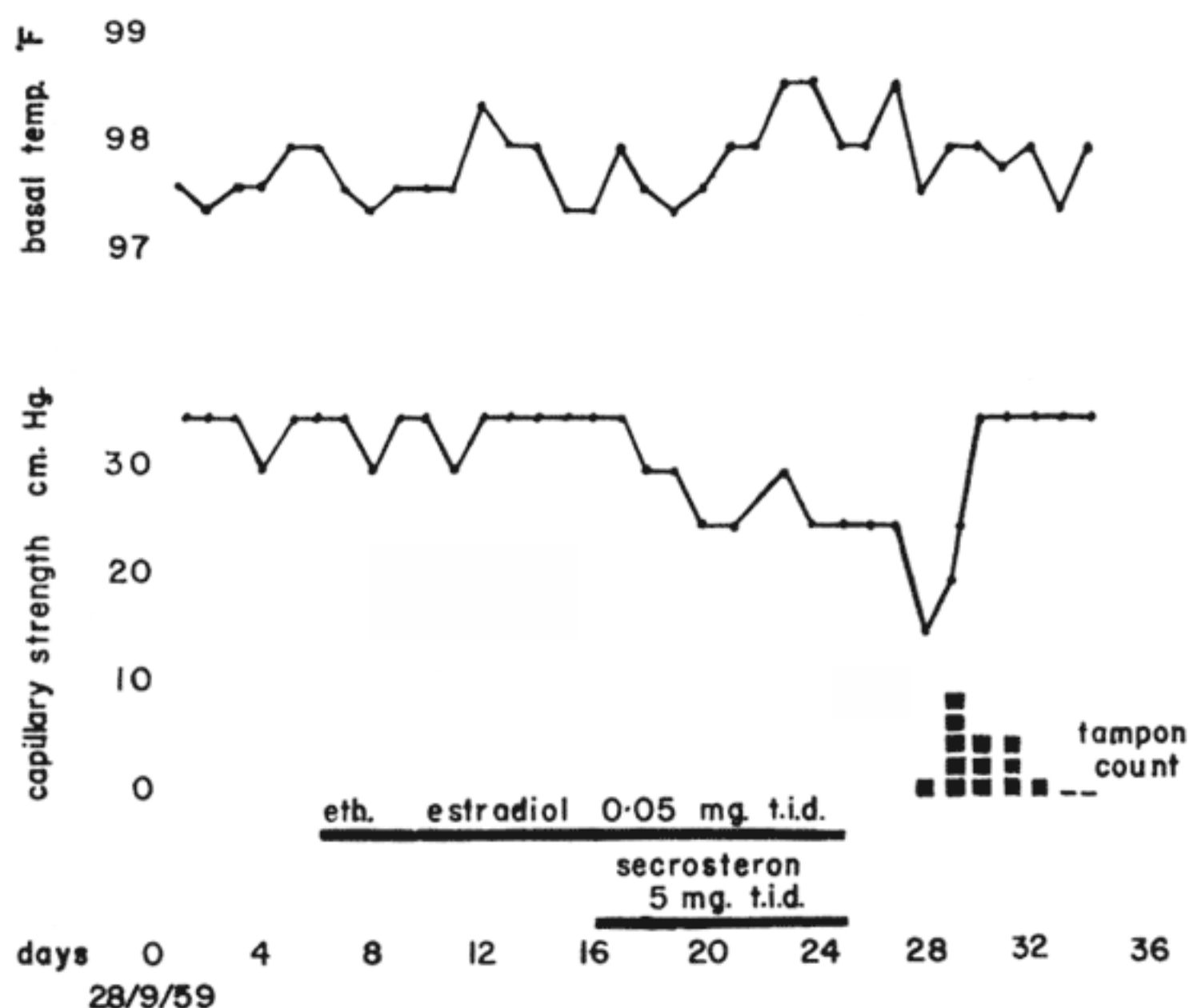


FIGURE 7. Basal body temperature and capillary strength of a 23-year-old woman (No. 22), with secondary amenorrhea of 2 years duration, who had proven thyroid and FSH deficiency. There were changes in capillary strength and withdrawal bleeding after oral estrogen and progesterone therapy.

seen in normal cycles, but that there was not the usual postovulatory drop, as ovulation did not occur.

Our studies of the effects of estrogens on the capillary strength have been limited by the difficulty of finding subjects with a persistently low capillary strength to act as test subjects. Postmenopausal women with "hot flushes" tend to have a low or a fluctuating capillary strength, but even among these women some are found whose capillary strength is normal.

In a selected group of 26 postmenopausal women between the ages of 45 and 55 who had persistently low capillary strength we have carried out test injections of conjugated equine estrogens (Premarin, Ayerst) 20 mg. in 5 ml. of normal saline. In 18 of 26, this resulted in doubling of the capillary strength either within a few hours as shown in FIGURE 8, or by the following day, and the effect usually persisted for about 2

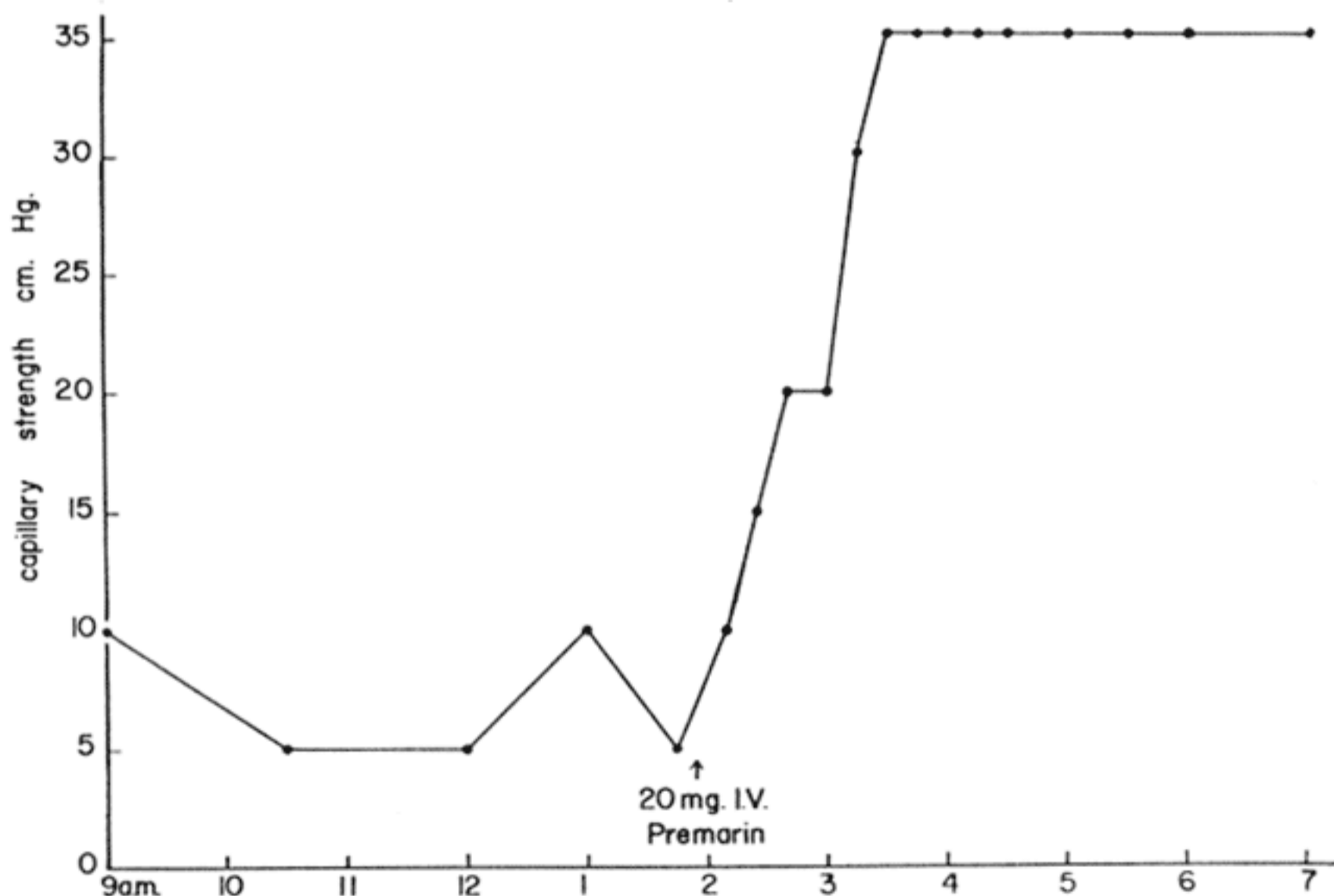


FIGURE 8. A graph showing the effect of an intravenous injection of 20 mg. of conjugated estrogens (Premarin, Ayerst) on the capillary strength of a postmenopausal woman with senile vaginitis.

days. The proportion of positive results seems to be much lower in younger or in older women; this work is continuing as a controlled experiment with tests carried out at similar intervals after normal saline injections.

The effect of oral ethinyl estradiol on capillary strength is clearly illustrated in FIGURE 9; this estrogen was administered in gradually

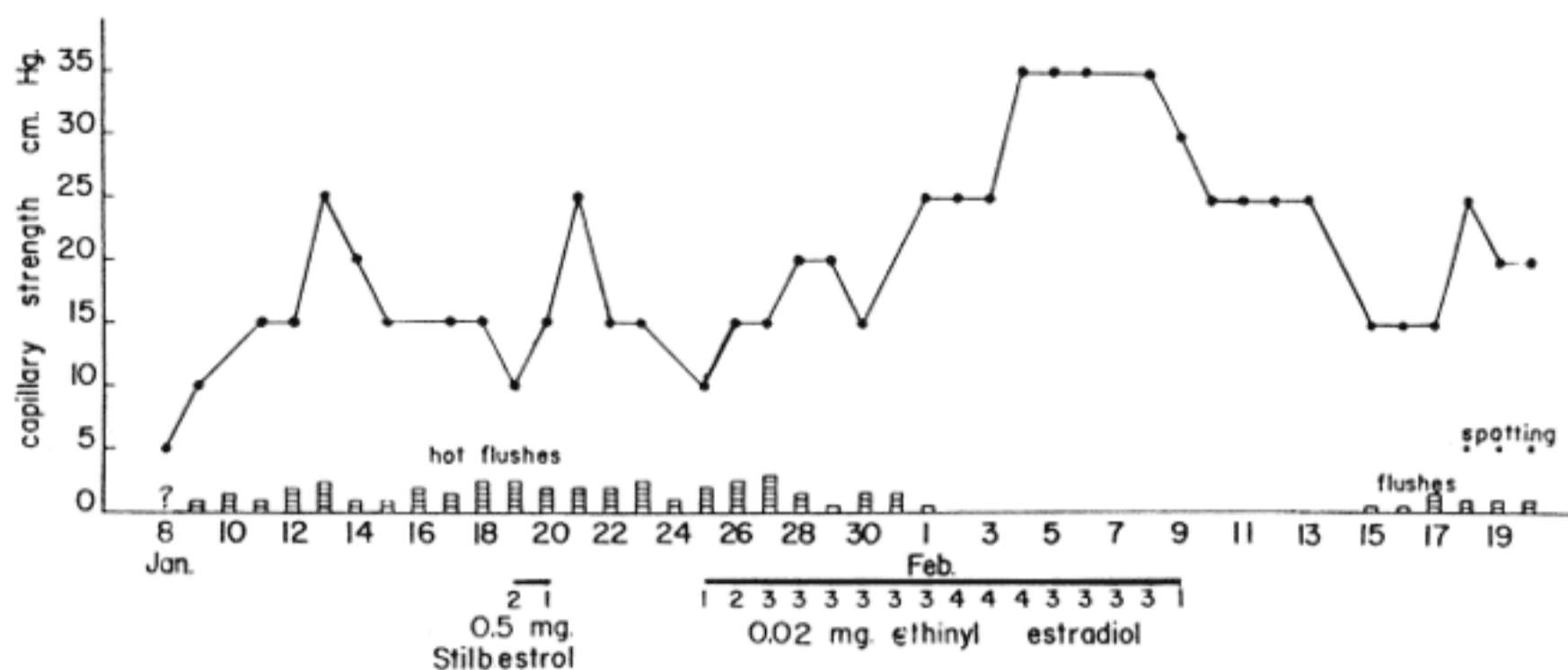


FIGURE 9. Changes in the capillary strength of a postmenopausal woman, before during and after oral estrogen therapy for hot flushes. The number of hot flushes reported by the patient each day is indicated by the number of steps in the ladders along the bottom of the graph.

increasing dosage to a postmenopausal woman with hot flushes; the minimum dosage required to elevate her capillary strength to 35 cm. Hg was 4 0.02 mg. tablets a day, but it may be noted that her hot flushes disappeared when the capillary strength had risen to 25 cm. Hg on 3 tablets a day.

The effect of a synthetic substance, Vallestril,\* in raising the capillary strength and abolishing hot flushes is shown in FIGURE 10. This substance is particularly interesting in that it has estrogenic properties, although it is quite different from the natural estrogens in chemical structure.

Preliminary investigations in this laboratory suggest that phenol itself causes a transitory elevation of the capillary strength, and that the acidic OH group may be the common denominator of many substances that fortify the capillaries. In this connection it is interesting that the basic counterpart of phenol, namely aniline and its derivatives such as acetophenetidine and acetanilide can cause purpura and/or menorrhagia.

### Discussion

A comparison of the daily output of estrogens during the normal menstrual cycle, reported by Brown, *et al.* (1959) and reproduced in FIGURE 11, with the daily capillary-strength changes in FIGURE 4 and 5 shows that the capillaries become fragile when the estrogen levels are falling, both after the ovulation peak and before menstruation. This fact, combined with the observation that the administration of estrogen to postmenopausal women raises their capillary strength, suggests strongly

\*Obtained from G. D. Searle & Co., Chicago, Ill.

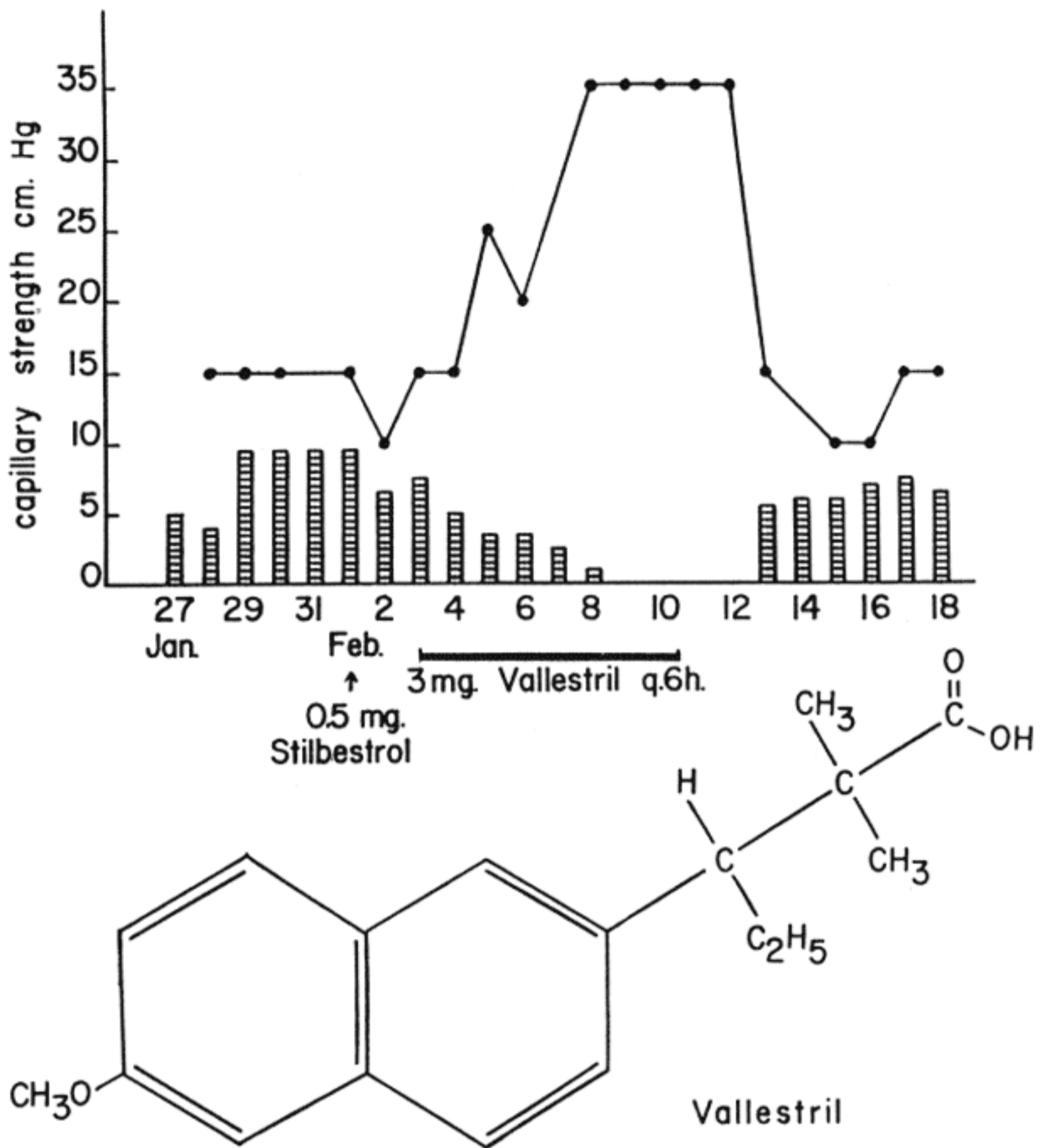


FIGURE 10. Graph showing the effects of Vallestril in raising the capillary strength of a postmenopausal woman and relieving her hot flushes. The number of hot flushes reported by the patient each day is indicated by the number of steps in the ladders along the bottom of the graph. The structural formula of Vallestril is shown here for comparison with those estrogens and proestrogens shown in FIGURE 13.

that estrogen withdrawal weakens the capillaries. Unfortunately we have not yet ascertained whether progesterone has any direct action on the capillaries or whether it acts only after conversion to estrogen, but the effect of estrogens and their withdrawal is quite evident; moreover it is a general effect involving the skin of the arms as well as the endometrium. The petechial hemorrhages of senile vaginitis may be an example of this phenomenon, as they are indicative of estrogen lack and respond very well to estrogen administration.

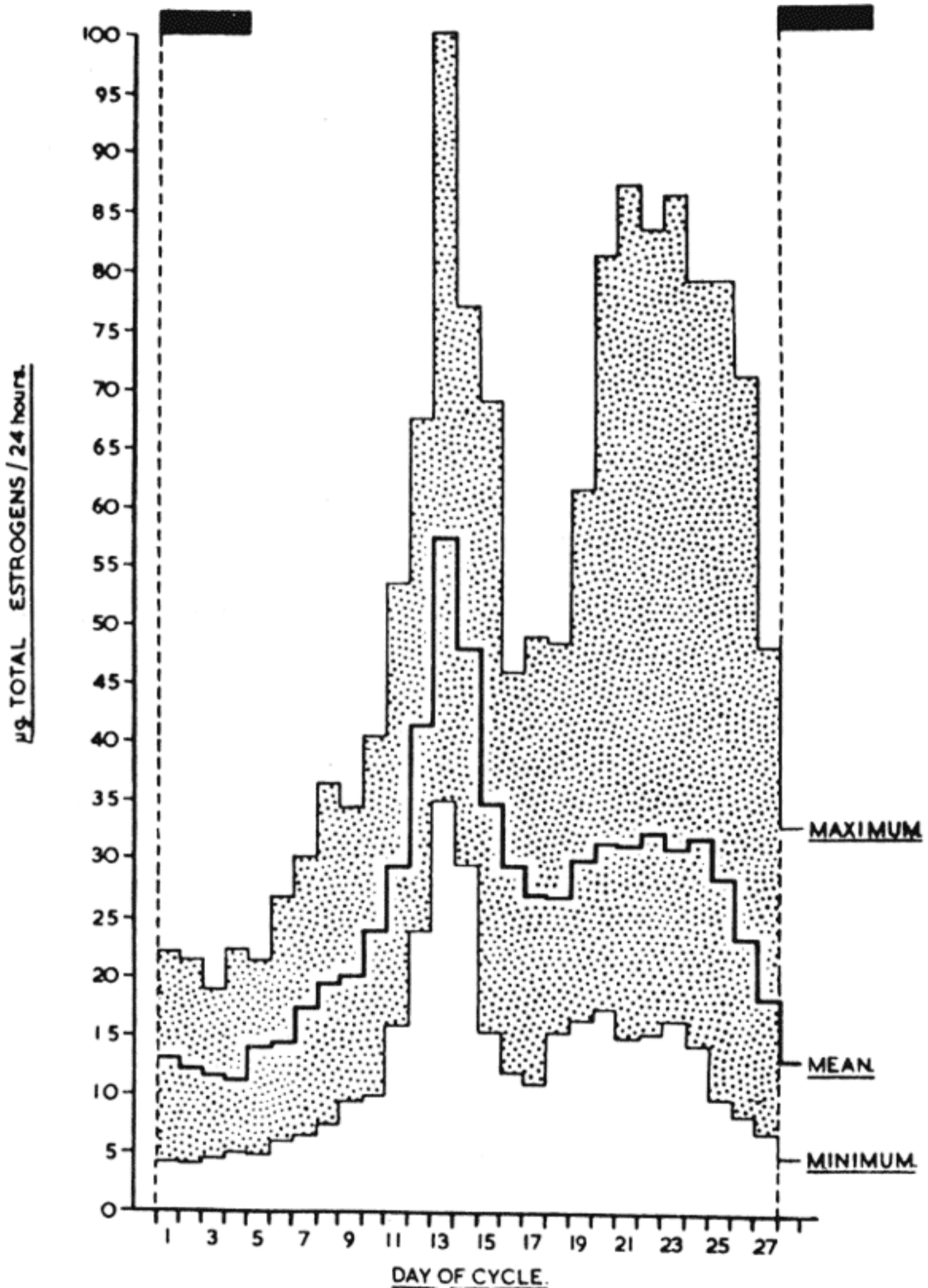


FIGURE 11. Mean total urinary estrogen output for each day of the menstrual cycle in 16 normal women. Reproduced from Brown *et al.* by permission of *The Journal of Obstetrics and Gynecology of the British Empire*.

Borchgrevink *et al.* (1960) were unable to detect any effect of Premarin on the bleeding time, clotting time, platelet count, platelet stickiness, or capillary fragility of any of the patients they studied, but they were using the tourniquet test, which is not suitable for repeated observations, and they did not select estrogen-deficient patients for their studies.

*Estrogens and the bioflavonoids.* Bennet's *et al.* (1946), in Australia, reported disturbances of reproduction associated with cystic hyperplasia of the endometrium in sheep that had been grazed on pastures dominated by an early flowering strain of subterranean clover. Subsequent work has shown that these sheep were obtaining estrogen from the bioflavonoid genistin in the clover.

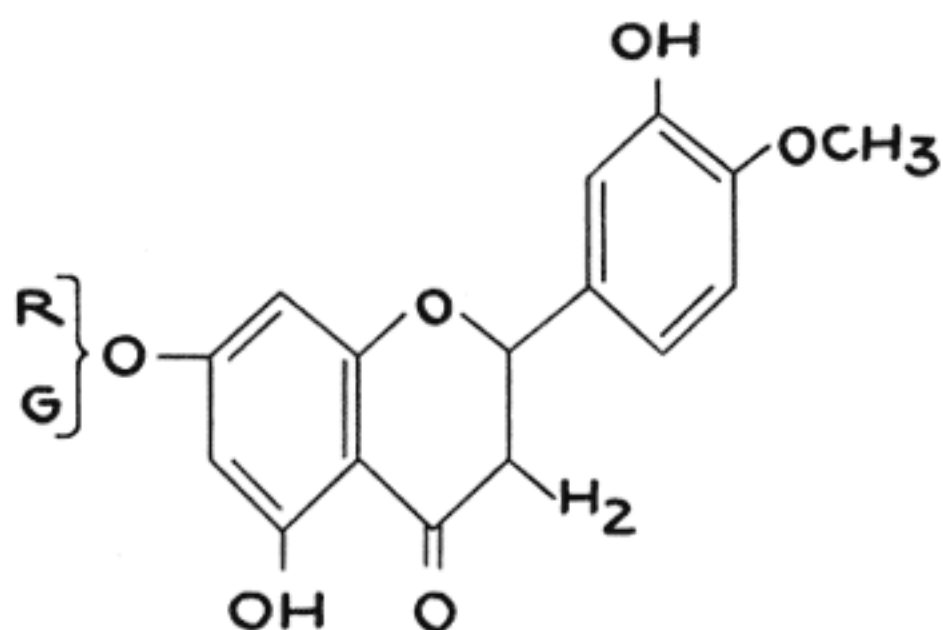
Since the original observation of Loewe (1928) that extracts of willow catkins and the ovaries of the water lily *Nuphar luteum* could cause estrus in ovariectomized mice, estrogenic activity has been reported in many plant substances, including the oil of palm kernels, the tubers of a chinese legume, alfalfa, hay, and soybean-oil meal. Skarzynski (1933) isolated estradiol from female willow flowers, but the estrogenic activity of many plants is due to substances that are precursors of the estrogens, rather than true estrogens.

Emmens (1942) studied the effects of estrogens and proestrogens on mouse vaginae that he had divided into two separate pouches. He found that the dose of a true estrogen that was just sufficient to cornify the epithelium of one pouch when placed on it, failed to produce cornification in the other pouch. However, an effective dose of a proestrogen for one pouch caused cornification in both pouches. It is evident that true estrogens act directly on the cells of the vaginal epithelium, while proestrogens must be absorbed into the body and give rise to estrogenic substances during their metabolism. Using this test Biggers and Curnow (1954) have shown that genistein (the aglycone of genistin) from subterranean clover, is a proestrogen.

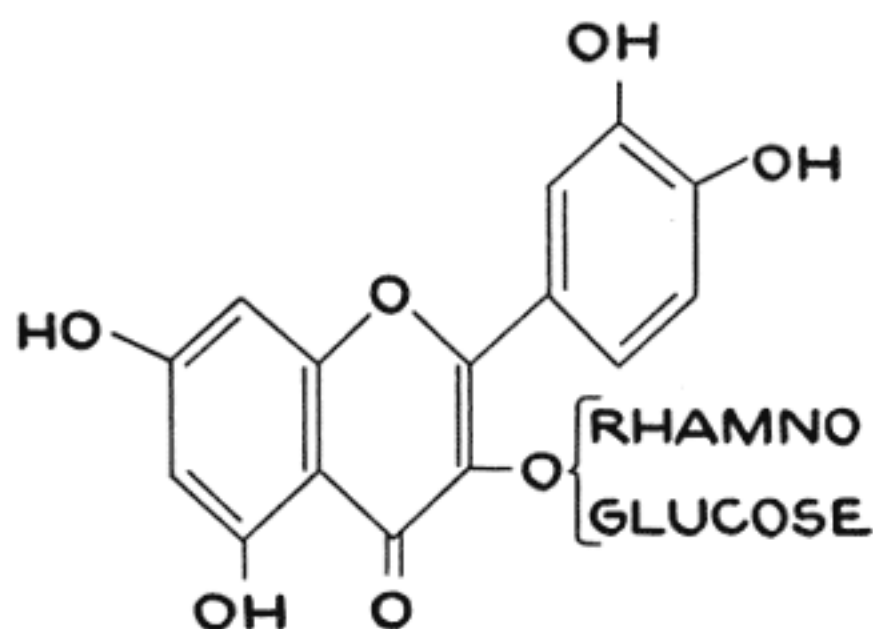
FIGURE 12 shows the chemical formulae of two natural bioflavonoids: hesperidin (Szent-Györgyi's citrin, or vitamin P), the bioflavonoid obtained from the peel of oranges and lemons, and rutin, which is obtained from buckwheat. There are many other bioflavonoids and, basically, they are all C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub> compounds.

FIGURE 13 shows the formulae of the natural ovarian hormone estradiol, the isoflavone genistein, and the synthetic estrogen diethylstilbestrol to illustrate the similarity of their structures, which are paralleled by some similarities of function. Cheng *et al.* (1955) have shown that the isoflavones daidzein, genistein, and biochanin A are estrogenic and have approximately 1/50,000th the estrogenic potency of stilbestrol. It is our conclusion that the estrogens are in some degree bioflavonoidal in that they strengthen the capillaries.

It is interesting to consider that the parallel between estrogens and bioflavonoids runs throughout both the animal and plant kingdoms. While the estrogens are responsible for many of the secondary sexual characteristics of animals, the bioflavonoids are responsible for the scents and the colors of many flowers, which may be considered as their secondary



**HESPERIDIN: FROM ORANGES AND LEMONS  
THE ORIGINAL CITRIN OR VITAMIN P OF SZENT-GYORGYI**

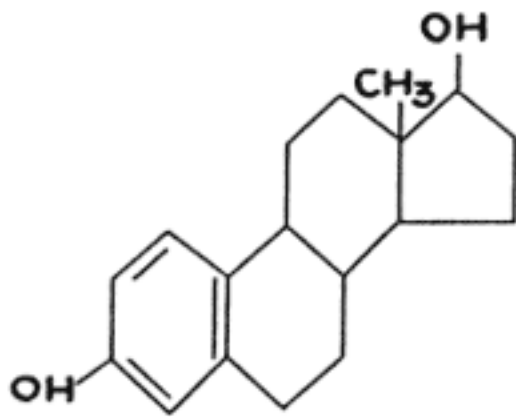


**RUTIN: FROM BUCK WHEAT**

FIGURE 12. The structural formulae of hesperidin and rutin are shown here for comparison with the estrogenic substances shown in FIGURE 13.

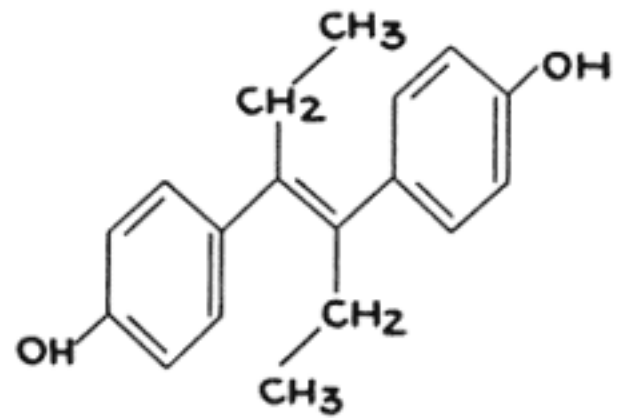
sexual characteristics. In fact this parallel goes as far back in both the animal and plant kingdoms as the protozoan organism *Chlamydomonas eugametos*, which may be one of their common progenitors. Moewus (1955) has studied sterile mutants of this organism and shown that their capacity for sexual reproduction can be restored by the addition of the bioflavonoid quercetin.

Szent-Györgyi (1955) has shown that the thymus contains a considerable quantity of an intensely yellow substance with many physical and chemical similarities to the bioflavonoid quercetin; it may be that the capillary integrity is normally maintained by this substance until puberty, when the gonads take over.



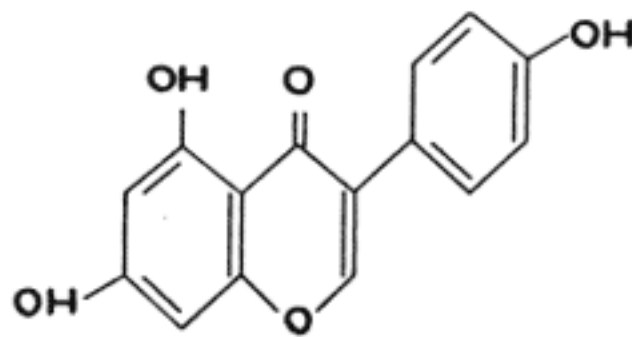
ESTRADIOL

A NATURAL OVARIAN TRUE ESTROGEN



DIETHYL STILBESTROL

A SYNTHETIC TRUE ESTROGEN



GENISTEIN

THE AGLYCONE OF GENISTIN, A NATURAL PLANT PRO-ESTROGEN

FIGURE 13. Structural relationships between a natural ovarian estrogen, a synthetic estrogen, and the natural plant, isoflavone genistein, which is a pro-estrogen.

*A theory of menstruation.* We know that several of the bioflavonoids are estrogenic, and evidence has been produced to show that the estrogens are in a sense bioflavonoidal in that they increase the strength of fragile capillaries.

It seems likely that the integrity of the capillaries is normally maintained by ascorbic acid and the bioflavonoids, but that the estrogens when present may compete with the bioflavonoids. Then, when the estrogen level falls or the estrogens are metabolized, the capillaries are left without support and become fragile until such time as the bioflavonoids can return to take their place in the capillary wall.

The work of Markee (1940) on the growth of endometrial transplants in the eyes of rhesus monkeys (FIGURE 14) correlates very closely with the estrogen excretion levels in the human menstrual cycle and with our own observations on capillary strength, for he showed a primary growth period during the proliferative phase of the cycle that was interrupted by a short period of regression at mid-cycle before the onset of a secondary growth period during the luteal phase. Moreover he showed that regression of the endometrium commenced five days before menstruation.

If estrogens temporarily replace the bioflavonoids in the capillary wall and continue to preserve the integrity of the capillaries until they

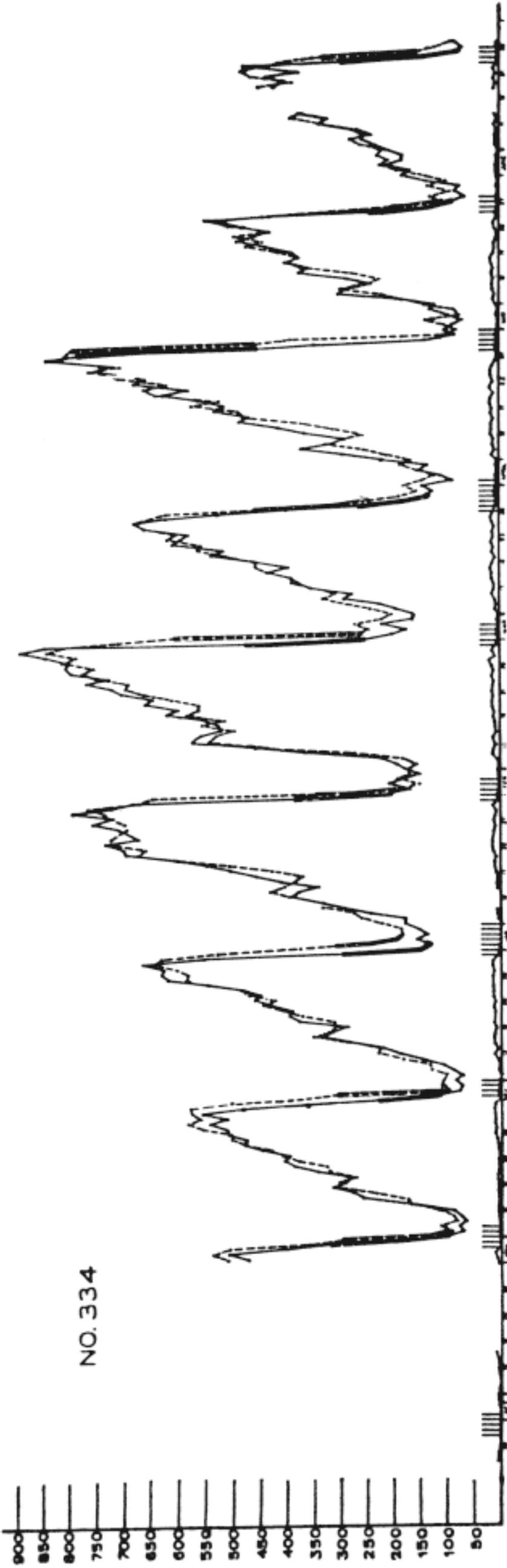


FIGURE 14. Graph of the area of an endometrial transplant in the anterior chamber of the eye of a rhesus monkey, showing the seasonal variation of an endometrial growth in this species. The interruption between the primary and secondary periods of endometrial growth at about the time of ovulation may be clearly seen in most of the cycles. Reproduced from Markee by permission of *Contributions to Embryology by the Carnegie Institute of Washington*.

are withdrawn, this would explain why a drop in the estrogen level causes bleeding but a persistently low or a persistently high estrogen level does not cause bleeding.

### *Summary*

Capillary fragility tests have been carried out by a suction method on the medial aspects of the upper arms of 33 healthy women during 42 menstrual cycles. The results show a consistent drop in capillary strength 2 days after ovulation and again 3 to 5 days before menstruation.

The postovulatory drop is as great, or nearly as great, as the premenstrual drop, but it is of shorter duration.

While the postovulatory drop usually lasts for 1 day, the premenstrual drop in capillary strength usually persists until the onset of menstrual bleeding.

Postmenopausal women with hot flushes tend to have a low or fluctuating capillary strength.

Intravenous administration of estrogens to postmenopausal women usually raises their capillary strength to normal, either within a few hours or by the following day.

It is postulated that the estrogens and possibly other steroids enter into competition with the bioflavonoids for a substrate in the capillary wall, where they maintain the integrity of the capillary until such time as they are metabolized or withdrawn.

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### *Addendum*

Since submission of this article for publication, a paper by Gordon W. Prueter has been published in which the author describes the beneficial effect of vitamin C and water-soluble citrus bioflavonoids in the treatment of menorrhagia. Prueter does not include any capillary strength studies in his report, but he has demonstrated the clinical efficacy of this treatment. Our own studies of the capillary strength of 41 patients with menorrhagia before and during treatment with vitamin C and bioflavonoids have now been submitted for publication elsewhere.

### *References*

- AINSLIE, W. H. 1959. *Obstet. and Gynecol.* 13: 185  
BARTELMEZ, G. W. 1957. *Am. J. Obstet. Gynecol.* 74: 931.

- BENNETTZ, H. W., E. J. UNDERWOOD & F. L. SHIER. 1946. *Australian Vet. J.* 22: 2.
- BENTSATH, A., S. RUSZNYAK & A. SZENT-GYORGYI. 1936. *Nature.* 138: 798.
- BIGGERS, J. D. & D. H. CURNOW. 1954. *Biochem. J.* 58: 278.
- BOINES, G. J. 1955. *Ann. N. Y. Acad. Sci.* 61(3): 721.
- BORCHGREVINK, C. F., R. ANDERSEN, J. HALL, K. HATTELAND & A. URSIN-HOLM. 1960. *Brit. Med. J.* 2: 1645.
- BREWER, J. I. 1938. *Am. J. Obstet.* 36: 597.
- BROWN, E. E. 1949. *J. Lab. Clin. Med.* 34: 1714.
- BROWN, J. B., R. KELLAR & G. D. MATTHEW. 1959. *J. Obstet. Gynecol. Brit. Emp.* 66: 177.
- CHENG, E. W., L. YODER, C. D. STORY & W. BURROUGHS. 1955. *Ann. N. Y. Acad. Sci.* 61(3): 652.
- EMMENS, C. W. 1942. *J. Endocrinol.* 3: 168; 174.
- GREENBLATT, R. B. 1955. *Ann. N. Y. Acad. Sci.* 61(3): 713.
- JACOBS, W. M. 1956. *Surg. Gynecol. Obstet.* 103: 233.
- JAVERT, C. T. 1955. *Ann. N. Y. Acad. Sci.* 61(3): 700.
- KRAMAR, J., V. W. MEYERS & D. J. PEETZ. 1954. *J. Lab. Clin. Med.* 43: 395.
- LOEWE, S. 1928. *Abstr. Ber. Wiss. Biol.* 7: 731.
- MARKEE, J. E. 1940. *Contrib. Embryol. Carnegie Inst. Washington* 28: 219.
- MARTIN, G. J. 1955. *Ann. N. Y. Acad. Sci.* 61(3): 646.
- MCMURRAY, G. A. & L. B. JAQUES. 1959. *J. Appl. Physiol.* 14: 813.
- MOEWUS, F. 1955. *Ann. N. Y. Acad. Sci.* 61(3): 660.
- PEPPER, H. & S. LINDSAY. 1959. *Obstetrics and Gynecology.* 14: 657.
- PREUTER, G. W. 1961. A treatment for excessive uterine bleeding. *Appl. Therapeutics.* 3: 351.
- REYNOLDS, S. R. M. 1949. *Physiology of the Uterus.* 2nd ed. :289. Hoeber. New York, N. Y.
- RINEHART, J. F. 1955. *Ann. N. Y. Acad. Sci.* 61(3): 684
- ROBSON, H. N. & J. J. R. DUTHIE. 1950. *Brit. Med. J.* 2: 971.
- SALVATORE, C. A. 1952. *Surg. Gynecol. Obstet.* 95: 13.
- SCHIFF, M. 1959. *Laryngoscope.* 69: 981.
- SHULMAN, M. H., L. C. WYMAN & G. P. FULTON. 1954. *J. Allergy.* 25: 28.
- SKARZYNSKI, B. 1933. *Nature.* 131. 766.
- STEPHAN, R. 1921. *Berl. Klin. Wochschr.* 58: 317.
- SZENT-GYORGYI, A. 1955. *Ann. N. Y. Acad. Sci.* 61(3): 732.
- VAN DER BURG, A. J. P. 1953. *Acta. Med. Scand.* 146: 448.
- ZACHARIAE, F. 1959. *Acta Endocrinologica.* 33: Suppl. 47.
- ZWEIFACH, B. J. 1955. *N. Y. Acad. Sci.* 61(3): 670.