A Metabolic Study of a Patient with Idiopathic Cyclical Thrombocytopenic Purpura

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CYCLICAL THROMBOCYTOPENIC PURPURA related to menstrual periods has been the subject of infrequent reports in the literature. Minot in 1936 first described three cases of purpura hemorrhagica associated with menstruation. He postulated that "some altered endocrine function" greatly exaggerating a drop of platelets thought to occur normally at the onset of menstruation might be responsible. No studies were performed to support this contention, however. The periodic episodes of thrombocytopenic purpura ceased spontaneously after from three to seven attacks in these patients. Recently Pepper, Liebowitz, and Lindsay reported another woman with this disorder. Their patient had an eight year history characterized by five attacks of localized purpura following delivery and three episodes of generalized purpura of the skin associated with menstruation. Repeated platelet counts demonstrated a fall in platelets to very low levels at the time of menstruation with a rise to higher, but still abnormally low levels during the mid-cycle. Endocrinologic studies including urinary 17-ketosteroids, 17-hydroxycorticosteroids and follicle stimulating hormone levels done during different phases of the menstrual cycle did not vary significantly, and thereby failed to implicate an endocrine factor.

The present study concerns a middle aged woman with an eight year history of intermittent episodes of thrombocytopenic purpura occurring cyclically in relation to her menstrual periods. In contrast to previous reports, however, our patient usually experienced purpura between her periods of menstrual flow. It was considered that the unusual nature of this patient's rare disorder warranted the extensive metabolic research study described in this report.

CLINICAL SUMMARY

R. G. was a 46 year old white housewife who was admitted to the Metabolic Unit of the UCLA Medical Center with a chief complaint of eight years of recurrent epistaxes, petechiae, ecchymoses, and other bleeding manifestations occurring cyclically at twenty-eight day intervals. In 1947 the patient noted the onset of menorrhagia. Three months later purpura of the lower extremities appeared. At that time her platelet count was found to be reduced and her bone marrow revealed nonfunctioning megakaryocytes. A diagnosis of idiopathic thrombocytopenic purpura was made and early in 1948 splenectomy was performed. This procedure was followed by a temporary rise in platelets, but shortly thereafter the purpura recurred. From that time to the present admission, the patient experienced intermittent episodes of bleeding manifestations which occurred at approximately twenty-eight day intervals, usually beginning mid-way between her menstrual periods and

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last from seven to ten days. Two or three times a year, however, her purpura coincided with her menstrual periods and during those times her menstrual flow was excessive. Three years prior to the present admission, hysterectomy and an oophorectomy were performed because of severe uterine hemorrhages. This operative procedure eliminated further uterine bleeding, but had no influence on her cyclic purpura. In addition to purpuric skin and mucous membrane lesions which appeared during the cyclic episodes, she often had severe epistaxes, occasionally had rectal bleeding, but never experienced symptoms suggestive of serious central nervous system hemorrhage. In addition to the operative procedures and numerous transfusions, various forms of therapy were attempted at several medical centers. ACTH, cortisone and cortisone-like drugs proved of some benefit in that they often decreased the severity of her bleeding manifestations. During the year prior to the present admission, prednisone was administered in divided doses of 30 mg. per day at the onset of each hemorrhagic episode and then gradually withdrawn as the purpura subsided. There was nothing in the patient's history to seriously implicate allergy as a possible etiologic factor.

Positive physical findings at the onset of her present hospitalization consisted of numerous petechiae, purpuric spots and ecchymoses scattered over her upper and lower extremities, her upper trunk, and to a lesser extent about her abdomen and buttocks. A few purpuric mucous membrane lesions were also seen. Her abdomen displayed well healed splenectomy and hysterectomy scars, and on pelvic examination a cervical stump was noted. Visible side effects of steroid therapy consisted of "moon facies" and a cervical fat pad.

Abnormal initial laboratory findings were a mild hypochromic anemia, a platelet count of 24,000 (the platelets appearing large and bizarre on the smear), a prolonged bleeding time, no clot retraction in twenty-four hours, and a bone marrow aspiration which revealed increased numbers of megakaryocytes without evident platelet production. The tourniquet test was markedly positive. Normal laboratory findings included urinalysis, stool examination, chest x-ray, clotting time, BUN, creatinine, fasting blood sugar, protein and A/G ratio, serum bilirubin (indirect and direct), thymol turbidity, cephalin flocculation, Coomb's test and VDRL serologic test for syphilis.

A detailed and extensive study was conducted in the Metabolic Unit in an effort to document the nature of the patient's history of cyclic hemorrhagic phenomena and to attempt to discover some hitherto unrevealed factor or factors which might lead to further understanding of the disease.

PROCEDURE AND METHODS

The patient remained under continuous observation in the Metabolic Unit throughout the course of this study. The prednisone she had been receiving prior to her admission was gradually withdrawn during the first three days of her hospitalization. Prednisone was not administered during the remainder of the study. Hemorrhagic skin and mucous membrane manifestations were carefully observed daily and recorded according to the degree of bleeding in a rough classification of from 0 to 4+. Laboratory observations made during the study are classified for convenience under the following three categories:

1. Hematologic

Hematologic observations consisted of platelet counts, complete blood counts, reticulocyte counts, total eosinophile counts, bleeding and clotting times, prothrombin consumption times, platelet agglutinations and bone marrow aspirations. Platelet counts were done almost daily. Two methods were employed, Fonio's indirect method and the Rees-Ecker direct method. Most of the other hematologic procedures were performed at one to five day intervals. The bone marrow aspiration was done three times during the study. Reticulocytes were counted using the dry method with brilliant cresyl blue, total eosinophile counts were done according to the method of Thorn et al., bleeding times were estimated by the Duke method, and coagulation times were done by the method of Lee and White. Prothrombin consumption times and platelet agglutinations were done according to the methods of Stefanni and Guerevitch and Nelken, respectively.
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2. Endocrinologic

Endocrinologic observations included the following urinary studies: 17-ketosteroids, 17-hydroxycorticosteroids, pregnanetriol, pregnanediol and gonadotropins (FSH). These determinations were repeated at frequent intervals throughout the period of observation. 17-ketosteroids were determined by a modification of the Zimmerman method, 17-hydroxycorticosteroids by a modification of the method of Brooks and Norymberski, pregnanetriol and pregnanediol by the method of Bongiovanni and Clayton, and gonadotropins (FSH) by preparing urine by the ultrafiltration method of Gorbman and assayed by the mouse uterine weight method of Levin and Tyndale. Cytologic assay of estrogenic activity was estimated by means of daily vaginal smears.

3. Metabolic

A modified metabolic balance study was instituted in addition to the other studies. During the time from the fifth through the thirty-fourth day of hospitalization the patient received exactly the same quality and quantity of food and liquid daily. The diet was a normal one established on the basis of the patient’s usual dietary habits. Her urine was collected in twenty-four hour aliquots and analyzed daily for sodium, potassium, chloride and uric acid. Sample diets duplicating the menu of the patient were prepared at intervals of five days, homogenized, sampled, and analyzed to determine intake of sodium, potassium and chloride. Blood was collected every five days in the postabsorptive state from an arm vein with the least possible stasis, and after prompt separation of the serum, determinations were made of sodium, chloride, potassium and uric acid. The analytic methods used were as follows: aliquots of diet and urine were ashed in a muffle furnace at a temperature not exceeding 450 C. Sodium and potassium determinations were performed directly on diluted specimens of urine and (blood) serum with the use of the Beckman flame photometer. Chlorides were determined by the Sanderson potentiometric method, and serum and urine uric acid by modification of the methods of Kalekar and Praetorius.

RESULTS

Clinical

The patient’s hemorrhagic manifestations were noted to increase for a few days following the discontinuance of prednisone (fig. 2), but then were observed to gradually fade and by the 19th day disappear altogether. Purpura recurred, however, on the 23rd day and gradually became worse, reaching its greatest severity by the 34th day. On the 36th day the hemorrhagic lesions again began to fade and by the 41st day were almost gone. Photographs (fig. 1) illustrate these changes. Thus the patient’s history of approximately a 28 day cycle of purpura was documented.

During the modified metabolic balance regimen the patient was weighed daily and it can be observed (fig. 4) that she gradually gained weight. It is felt that this weight gain reflected an error in estimating the proper maintenance caloric intake.

Hematologic

Table 1 and figure 2 show the hematologic data. The platelet variations are striking in that they were very low at the time of admission, then rose rapidly to a peak which reached its maximum on the 21st day. This was followed by a rapid fall over a seven day period to the initial very low levels. In addition, it can be observed that the platelets again were increasing during the last few days of the patient’s hospitalization. The platelet changes were most striking by the indirect method. The values obtained with the direct method demonstrated a
Fig. 1.—Photographs demonstrating the rapid disappearance of the hemorrhagic skin lesions. A was taken on the 36th day of hospitalization when the platelet level was very low. B was taken on the 42nd hospital day at a time when the platelet level had begun to rise.

similar rise and fall. The platelet changes correlated well with the bleeding and prothrombin consumption times. Clot retraction was absent at the times platelets were low. Clotting times were noted to be slightly prolonged at a time when the blood platelets were very low. No significant variations were observed in the hemoglobin, hematocrit or reticulocytes. The red blood cell counts, however, fell gradually to slightly lower levels by the end of the study. White blood cell counts and differential counts also failed to show significant cyclical variations. Total eosinophile counts were high initially at a time when platelets were reduced, then were seen to fall gradually as the platelets increased. No rise was
MINUTES

30 BLEEDING AND CLOTTING TIMES I

BLEEDING STILL PROFUSE—STOPPED BY TECHNICIAN

CLOTTING TIME

METABOLIC BALANCE

PER C. mm.

300,000

250,000

200,000

150,000

100,000

50,000

0

PLATELET COUNTS

DIRECTION METHOD

INDIRECT METHOD

CLOT RETRACTION

PER C. mm.

300

200

100

0

TOTAL EOSINOPHILE COUNT

PURPURA

GRAPICALLY ILLUSTRATED

HOSPITAL DAYS

848
* Includes data not shown in figure 2 only.

seen, however, when the platelets again fell. Platelet agglutinins were consistently negative throughout the study. Bone marrow aspirations done initially, just

Fig. 2.—Graphs illustrating some of the hematologic data accumulated during the study.
Fig. 3.—Graphs illustrating the endocrinologic data observed during the study.

Fig. 4.—Graphs illustrating metabolic data accumulated while the patient was on a constant food and fluid intake. The dietary lines represent averages of dietary analyses determined every five days. True metabolic balance is not demonstrated in the electrolyte studies, as fecal excretion studies were not performed. (Fecal sodium and chloride excretion normally is negligible as compared to the urinary excretion. Fecal potassium excretion is usually somewhat higher, but also is small as compared to normal urinary excretion.)
before the platelet peak, and just after the platelets began to fall, all revealed increased numbers of inactive appearing megakaryocytes. There were no significant differences between the three marrow aspirates.

**Endocrinologic**

Figure 3 shows the endocrinologic changes. Urinary 17-ketosteroid excretion was somewhat low, but no cyclical fluctuations were demonstrated. Urinary 17-hydroxycorticosteroids also failed to reveal variations significant enough to suggest cyclical differences in adrenal activity. Urinary gonadotropins (FSH) done four times during the cycle were definitely low at the time the platelets began to fall just after the maximum peak. Pregnanediol and pregnanetriol determinations were all within the normal limits. Vaginal smears for cytologic study revealed low estrogenic activity in the vaginal epithelial cells throughout the observation period. No cyclical ovarian estrogenic activity was observed.

**Metabolic**

Figure 4 reveals the metabolic data. The fluctuations in urinary electrolyte excretion can be considered within normal limits. No cyclical variations are evident. The serum values remained fairly constant throughout. Daily urinary uric acid excretion also remained constant. Serum uric acid, however, was...
observed to be considerably higher than normal while the platelet levels were rising, then fell as the platelets fell. A final high value of 10.1 mg. per cent was obtained shortly before discharge at a time when the platelets were again observed to be rising.

In conclusion, our observations have documented the patient's cyclical thrombocytopenia and associated hemorrhagic manifestations. No cyclical estrogenic activity was demonstrated by the vaginal cytologic technic and the pregnanediol and pregnanetriol determinations. The urinary gonadotropins, however, were very low at a time when the platelets had begun to fall just after reaching their maximum peak. Urinary 17-ketosteroids, 17-hydroxycorticosteroids and electrolyte excretion patterns failed to show cyclical variations. Serum uric acid levels, however, did appear to show a cyclical variation. Figure 5 illustrates the variations in platelets, urinary gonadotropins and serum uric acid superimposed on the same graph in order that the time relationships of the changes can be more readily observed.

Discussion

The diagnosis of thrombocytopenic purpura was established in our patient by the low platelet count, the presence of large and bizarre platelets, increased megakaryocytes showing inactivity in the bone marrow, prolonged bleeding time, absent clot retraction, poor prothrombin consumption and positive tourniquet tests. The lack of a demonstrated etiologic factor or factors would continue its classification in the idiopathic group. The cyclic nature of her thrombocytopenia was established in this study.

Cyclical platelet fluctuations are known to occur normally in association with the menstrual cycle. Genell\(^1\) and later Pohlo\(^2\) demonstrated these fluctuations in studying the menstrual cycles of a large number of normal women. Platelets were found to be lowest at the time of menses, and highest during the mid-cycle. Recently, Pepper and Lindsay\(^3\) reported similar observations in their study of twenty-six normal women. Using the Rees-Ecker method of counting platelets, they found that platelet levels varied between 70,000/cu.mm to 462,000/cu.mm with a mean of 217,000/cu.mm. Day to day fluctuations usually ranged no more than from 5,000 to 30,000. They found the highest levels at the mid-cycle, sometimes with a dramatic peak, and showed that this highest level often coincided with ovulation.

Attempts have been made to implicate endocrine factors in the etiology of normal platelet fluctuations. Genell\(^1\) was unable to show that estrogen levels had anything to do with platelet variations. He felt that the decline of platelets at the onset of menstruation may be related to the extinction of the corpus luteum that takes place at that time, and that the increase in platelets after menstruation reflected a reaction of the organism to necrosed material.

Cortisone and ACTH have been shown to increase capillary resistance\(^4\) and have proved useful in the treatment of idiopathic thrombocytopenic purpura. Variations in capillaries of normal subjects have been studied by Brewer.\(^5\) He found that on the first and second days of menstrual flow there is uniformly an
increase in capillary fragility. During the remaining days capillaries become more resistant. Interestingly, however, in numerous instances there is a brief period of increased capillary fragility near the midpoint of the cycle.

The reported cases\textsuperscript{1,2} of idiopathic cyclical thrombocytopenic purpura occurring in women would appear to reflect a marked exaggeration of the platelet and perhaps capillary fluctuations normally observed in association with the menstrual cycle. In our patient, however, the purpura, by history, usually appeared midway between the menstrual periods, suggesting a different etiologic mechanism or mechanisms. The lack of functioning ovarian tissue, as shown by the cytologic vaginal smears and the pregnanediol and pregnanetriol determinations, would appear to rule out these glands as being etiologically involved. Indeed, cyclical thrombocytopenia has been reported by Demmer\textsuperscript{26} in a man of 61 who had attacks of thrombocytopenia and purpura regularly predictable at 28 day intervals for six years prior to his death as a result of chronic nephritis.

Cyclical changes in adrenal activity were not demonstrated by urinary 17-ketosteroid or 17-hydroxycorticosteroid variations. Urinary and serum sodium, potassium and chloride values determined while the patient was receiving a constant daily intake of food and fluid also revealed no variations which might reflect cyclical adrenal activity. Total eosinophile counts were highest just before the platelets began to rise, and were lowest at the time the platelets reached their peak. They failed, however, to rise again to their initial high levels with the subsequent fall in platelets and thus demonstrated no cyclical variation. The rise in eosinophils during the initial part of the study may have been due to a transient period of adrenal cortical insufficiency following prednisone withdrawal.

Urinary gonadotropins (FSH) dropped markedly at a point just after the platelets had reached their peak. This finding suggests that the pituitary might be implicated in some type of cyclical change in activity whether primary or secondary in origin. It would have been of great interest if the patient could have been observed through another cycle and the FSH depression demonstrated again.

The serum uric acid values also appear to vary in a cyclical fashion. Urinary excretion of uric acid, however, showed no significant variations. A possible explanation for the high serum values is that they reflected the breakdown of erythrocytes at sites of hemorrhage. Increased red blood cell production at these times may have been an additional contributing factor. The relatively constant urinary excretion of uric acid despite the variations in serum values may have been related to the inability of the patient's renal tubular reabsorptive mechanisms to handle an increased load of uric acid. Although gross tests of renal function failed to reveal abnormalities, another possibility is that an undisclosed renal defect was present which prevented uric acid excretion to exceed the relatively constant excretion levels obtained.

**SUMMARY**

A woman with a history of thrombocytopenic purpura occurring approximately every twenty-eight days was studied extensively on the Metabolic Re-
search Ward. The patient had been treated previously with splenectomy and hyster-o-ophorectomy without improvement. The cyclical nature of her thrombocytopenia was documented by repeated hematologic observations. Endocrinologic studies demonstrated no evidence of ovarian activity or cyclical variations in adrenal activity. Urinary gonadotropins (FSH) fell coincident with the fall in platelets and suggest that cyclical pituitary function might be related in some way. The exact etiologic mechanisms, however, were not disclosed by this study.

**SUMMARIO IN INTERLINGUA**

Un femina con un historia de purpura thrombocytopenic occurrente approximativemente omne vinti-octo dies esseva studiate extemensente al Section pro Recercas Metabolic. Le patiemste habeva previemente essite tractate per splenectomy e hyster-o-ophorectomy sin resultante melioration. Le natura cyclic de su thrombocytopenia eseva documentate per repetite observationes hematologic. Studios endocrinologic demonstrava nulle activitate ovarian e nulle variationes cyclic del activitate adrenal. Le gonadotropinas in le urima (i.e. le hormon de stimulation follicular) se reduceva in coincidentia con un reduction del plachettas. Isto pare indicar que un function cyclic del glandula pituitari es interessate in alicun maniera in le phenomeno. Tamen, le exacte mechanismos etiologic non eseva clarificate per le presente studio.

**REFERENCES**

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