Iron Deficiency in Gynecologic Patients

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IRON deficiency anemia among adults in the United States occurs almost exclusively as a result of chronic blood loss. In the absence of blood loss, inadequate iron intake can lead to anemia only after prolonged deprivation. Dietary restriction of iron may become limiting under circumstances in which requirements are increased, as during pregnancy, lactation, the rapid growth of infancy and childhood, or with chronic mild hemorrhage such as excessive menstruation. The present study illustrates the nature of this blood loss effect on the therapeutic response to iron and to iron plus other hemopoietic preparations in the management of metorrhagically induced iron deficiency anemia. From these data, we have attempted to estimate the quantity of iron lost by the woman with repetitively excessive menstrual blood loss which has led to anemia, the amount of iron required to replace this deficit, and finally, whether factors other than iron reinforce or enhance the hemopoietic response in such a person.

MATERIAL AND METHODS

Only women in their reproductive period of life were entered in the study. Their composition by race, age and weight is presented in Table I. All patients had confirmed evidence of iron deficiency anemia. The criteria included: a mean cell volume (MCV) of less than 75 cu.μ. and/or a mean cell hemoglobin concentration (MCHC) of less than 30 per cent. Nineteen of the patients revealed evidence of iron deficiency by both criteria. In twenty-five women only hypochromia was present. In the remaining six persons microcytosis was the predominant feature.

In all instances the cause of excessive blood loss was menstrual disorders associated with benign pelvic conditions, i.e., functional uterine bleeding due to endocrine failure or uterine tumors such as fibroids and polyps. Women who were pregnant, had aborted, or were lactating, or who had gynecologic malignancies were not included in the present study. Of the group, ten patients came to final operative treatment during the observation period for the management of their gynecologic disorders. Such treatment consisted of dilatation of the cervix and curettement of the uterine endometrium or total abdominal hysterectomy.

Patients accepted for the study had three baseline evaluations on three successive days prior to initiation of therapy. The red blood count (R.B.C.), hemoglobin (Hb) and packed cell volume (PCV) were measured on venous blood treated with mixed potassium and ammonium oxalate, and the procedures were carried out within twenty minutes of obtaining the sample. Wintrobe's blood indices were calculated. Reticulocyte counts were made on capillary blood using wet preparations. Hemoglobin was determined photoelectrically by the cyanmethemoglobin method.[1] The packed cell volume[2] was measured in Wintrobe hematocrit tubes after being centrifuged at 3,000 r.p.m. for thirty minutes. Erythrocytes[3] were counted in duplicate after mixing with Hayem's solution.

Following the initial determinations each patient was assigned alternately to one of the therapy groups on the basis of her initial hemoglobin level (Table II). The duration of hematologic observations during therapy averaged eleven weeks and ranged to twenty-four weeks, while post-therapy follow-up has extended an additional one to two years. Fifty persons

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received encapsulated ferrous sulfate orally in dosage levels equivalent to 60, 100 or 300 mg. per day of elemental ferrous iron. There were seventeen additional women similarly studied, six of whom received an oral liver concentrate elixir containing the equivalent of 60 mg. of elemental iron and eleven who received the liver concentrate plus added ferrous sulfate to bring their total iron intake to 100 mg. of ferrous iron per day. During therapy blood values including reticulocyte counts were determined daily for the first two weeks. Subsequently biweekly (for six weeks) and weekly (for three months) observations were made. Each patient returned immediately following the completion of her menses for hematologic assessment.

This report presents primarily the results of the iron therapy groups. As the liver concentrate contained some iron (60 mg. elemental iron per day) and other possible hemopoietic substances, there was the opportunity to compare the efficacy of iron therapy with a "shotgun type" of hematinic. By analysis this liver concentrate supplied daily:

Iron . . . . . 60 mg.	Pyridoxine hydrochloride . . . . 1 mg.
Copper . . . . 1.8 mg.	Pantothenic acid . . . 8.7 mg.
Riboflavin . . . 2.8 mg.	Vitamin B_{12} . . . . 20 μg.
Niacin . . . 27 mg.	Inositol . . . . . 30 mg.
Thiamin . . . 2 mg.	Choline . . . . . 60 mg.

All the essential members of the vitamin B complex are present in amounts at least equal to the National Research Council's Recommended Allowances.[4] All iron, liver and liver plus iron therapy was administered orally in three divided daily doses.

RESULTS

Classification of the patients by therapeutic dosage level of iron and initial hemoglobin value is presented in Table II. It may be noted that all fifty patients had hemoglobin values of 10 gm. or less per 100 ml., and evidence of hypochromia and/or microcytosis. The erythrocyte count was more than 4 million in twenty-four patients, between 3.9 and 3.5 million in twelve, and less than 3.5 million in the remaining fourteen. While blood volume determinations were not made in this group, evidence from the literature[5] indicates that chronic blood loss of the nature here studied is not associated with appreciable changes in the total blood volume. Calculated blood volumes based on 66 cc. per kg. of body weight[6,7] are shown for these somewhat obese women in Table I.

Eleven patients did not experience additional menstrual loss during their period of therapy and observation. In the remaining thirty-nine patients it is possible to calculate a minimal iron loss during menses per period during therapy. This calculation is based on the observed changes in hemoglobin concentration as a result of menstruation and the estimated blood volume. The accepted normal menstrual blood

TABLE I

Iron Deficiency in Gynecologic Patients, and Treatment

Dosage of iron (mg.) per day	60	100	300	
Number of cases	19	14	17	50
Negro	12	5	9	26
White	7	9	8	24
Age (yr.)				
Mean	37	34	37	36
Range	22–50	20–45	22–44	20–50
Weight (kg.):				
Mean	71	69	66	69
Range	50–96	50–105	50–96	50–105
Calculated blood volume (L.):				
Mean	4.6	4.6	4.2	4.6
Range	3.3–6.3	3.3–6.9	3.3–6.3	3.3–6.9

NOTE: Figures in last column represent totals.

TABLE II

Distribution of Initial Hemoglobin Concentrations

Dosage of iron (mg.) per day	60	100	300	
Number of cases	19	14	17	50
Hemoglobin (gm./100 ml.):				
<6.0	2	2	2	6
6.0–6.9	2	1	1	4
7.0–7.9	3	4	1	8
8.0–8.9	2	2	6	10
9.0–9.9	4	3	6	13
>10.0	6	2	1	9

NOTE: Figures in last column represent totals.

TABLE III

Calculated* Minimal Iron Loss per Menstrual Period During Therapy

Dosage of iron (mg.) per day	60	100	300	
Number of cases	19	14	17	50
Iron loss (mg.) per period:				
Nil†	3	3	5	11
<39 (14)	2	2	3	7
40–79	2	1	3	6
80–119	5	3	1	9
120–159	1	1	1	3
160–199	1	2	3	6
200–239	1	0	1	2
>240 (313)	4	2	0	6

NOTE: Figures in last column represent totals.

* Calculated from decrease in hemoglobin concentration during menses and estimate of blood volume.

† Amenorrheic or postoperative.

loss is from 35 to 70 ml. per period. This is equivalent to 14 to 28 mg. of elemental iron per period. It is evident (Table III) that in the study group the amount of blood and resultant iron loss was considerably in excess of 28 mg. of iron per period. Only one patient had losses in the accepted range of normal (14 mg.) while the greatest blood loss amounted to over 300 mg. of iron per period. This latter would be equivalent to 750 ml. of whole blood being lost per menses. These estimates refer to decreases in total body iron. Expressed as quantities of iron in the diet necessary to meet the losses, taking into account absorption and utilization, they would represent the metabolism of up to 10 mg. of elemental iron per day, or a tenfold increase over normal uptake of iron from dietary sources.[8]

The average hemoglobin responses of the persons receiving one of the five therapeutic agents are shown in Figures 1 through 6. Each chart represents the results of therapy during the initial ten weeks of observation among persons with similar initial levels of hemoglobin deficit.

As expected, the level of reticulocytosis was correlated to the initial hemoglobin value. The minimal response observed was 1.7 per cent and the maximum 18.6 per cent. There was no appreciable difference in the degree of response by the various levels of therapeutic iron. The average reticulocyte peak was 5.0 per cent for the 60 mg. of iron, 6.4 per cent for the 100 mg. level, and 5.7 per cent for those receiving 300 mg. of iron. The day of peak response was somewhat earlier in the group taking the lowest iron dosage than in the other two (mean time, 60 mg. at the sixth day, 100 and 300 mg. group on the tenth day of therapy). This difference is probably not physiologically meaningful.

Of equal interest is the length of time required for relapse once therapy was discontinued. Among the thirty-nine patients who continued to have excessive menstrual blood loss with each period there was no difference in relapse time whether they had received 60 mg. of elemental iron (34 to 590 plus days), 100 mg.

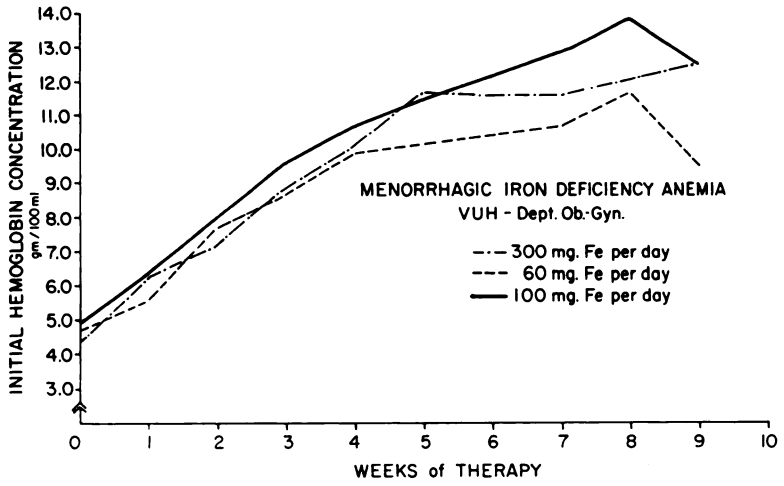

FIG. 1

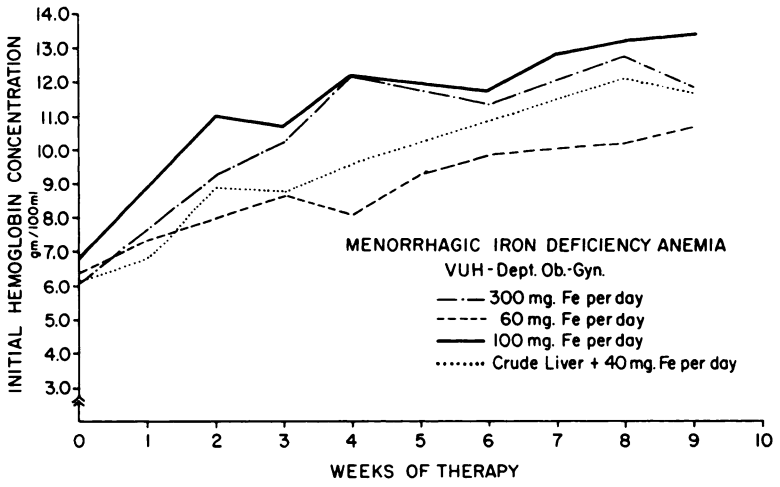

FIG. 2

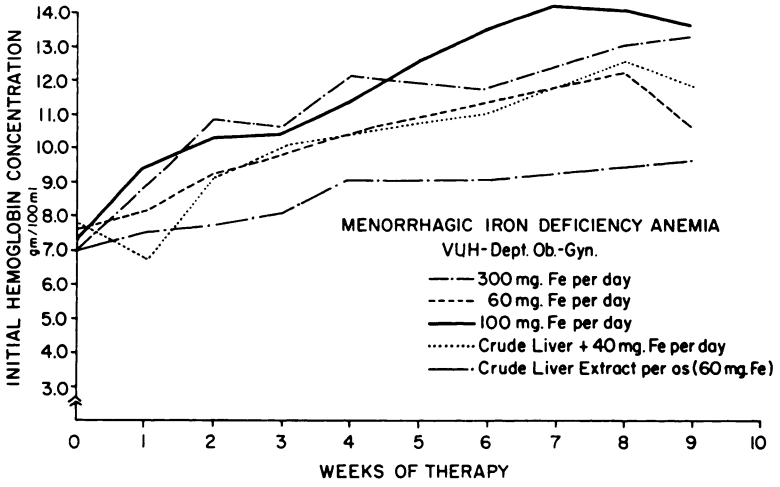

FIG. 3

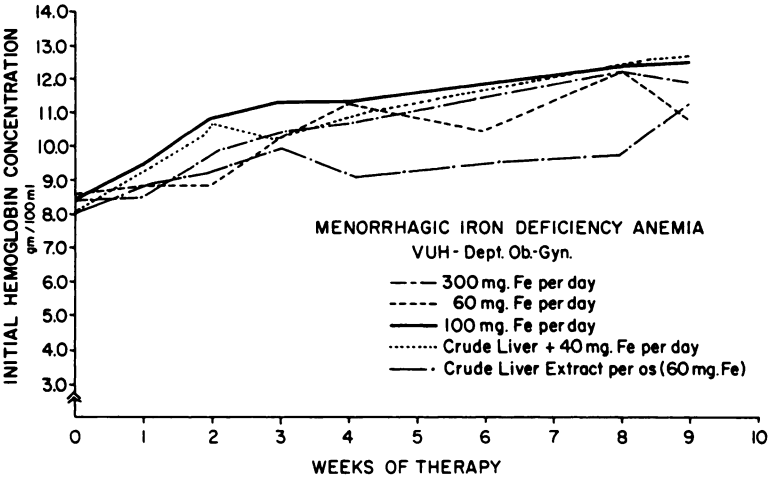

FIG. 4

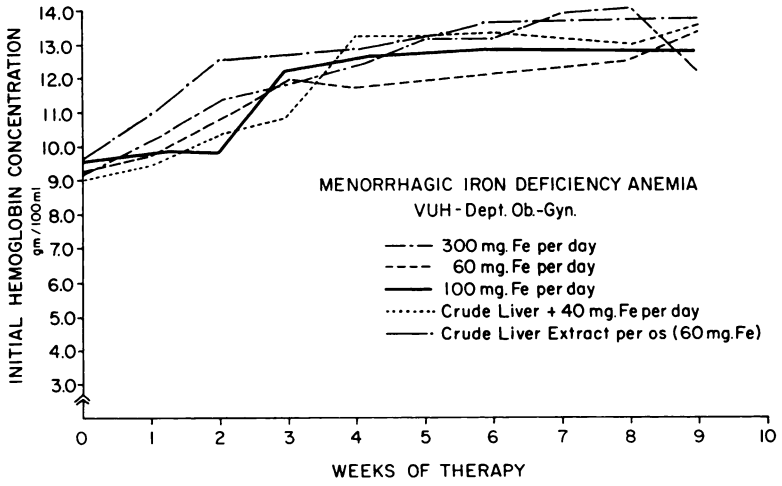

FIG. 5

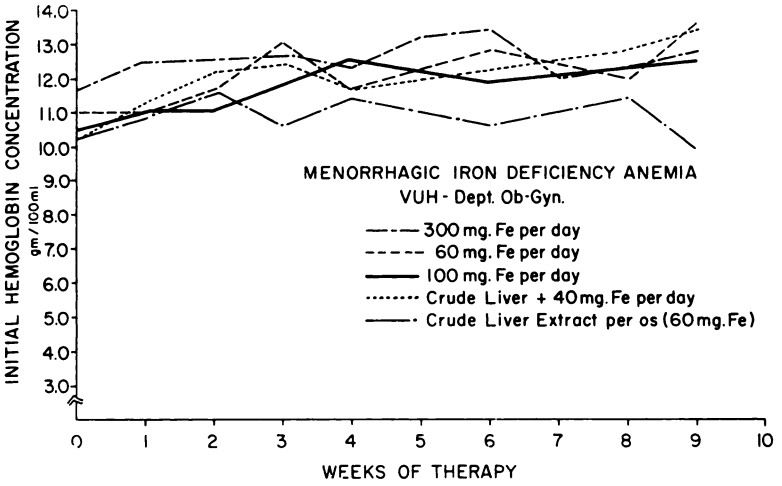

FIG. 6

(31 to 620 plus days) or 300 mg. (22 to 470 plus days). Obviously the time of relapse was dependent on the patient continuing to lose blood through menstruation and the amount of blood loss associated with these menses. As there were no appreciable differences among the groups in their calculated iron loss from menses (Table III) iron dosage level did not influence the time required for hematologic relapse.

The initial therapeutic responses show that regardless of iron dosage level the hemoglobin concentration can be raised from as low as 4 gm. per 100 ml. to values in excess of 10 gm. per 100 ml. within four weeks (twenty-eight days) after the initiation of iron therapy. These data (Figures 1 to 6) indicate that: (1) The maximum effectiveness is achieved with therapeutic iron at the level of 100 to 300 mg. per day. (2) No superiority in initial response or relapse time can be demonstrated for the 300 mg. per day iron dosage. (3) No difference in therapeutic efficacy exists between 100 mg. of iron alone and the liver concentrate (containing 60 mg. of iron per day plus a variety of other nutrients and an added 40 mg. of iron). (4) Persons taking 60 mg. of iron had slower rates of hemoglobin regeneration than did those receiving 100 mg. or more, and it would appear that this dosage level (60 mg.) is not adequate for maximal regeneration in the presence of repetitive menstrual loss. (5) Patients re-

ceiving liver alone (containing 60 mg. of elemental iron per day) showed no superiority to those taking similar levels of iron alone. Actually they exhibited the lowest degree of hematologic response.

In the correction of the blood indices (MCV and MCHC) in response to iron therapy it is noteworthy that the microcytosis was invariably corrected first and that the hypochromia changed more slowly. Hypochromia in subsequent relapse presented as the first evidence of recurring iron deficiency. Hypochromia is a more sensitive index of iron deficiency anemia than is microcytosis.

In a further attempt to appraise the relative merits of the three dosage levels of iron, the average increase of hemoglobin concentration per week after the initiation of therapy but prior to the onset of additional menstrual blood loss has been calculated and is presented in Table IV. The groupings are based, as previously, by initial hemoglobin level and level of therapeutic iron. The inferior performance of 60 mg. of iron is further evident in these data. The over-all average rate of hemoglobin regeneration to the three dosage levels was 1.1 gm. per 100 ml. per week. The rate of response among women with less than 6.0 gm. of hemoglobin compares favorably with maximal rates (1.82 gm. per 100 ml. per week) of regeneration reported for parenterally administered massive doses of iron.[9] It is apparent that the rate of regeneration per week decreased as the initial hemoglobin concentration approached more normal values.

TABLE IV

Average Increase in Hemoglobin Concentration per Week During Treatment and Prior to Onset of Menstrual Loss

Dosage of iron (mg.) per day	60	100	300	
Number of cases	19	14	17	
Initial hemoglobin concentration (gm./100 ml.):	Mean Hemoglobin Gain (gm./wk.)			
<6.0	1.8	1.9	1.7	1.8
6.0–6.9	0.9	1.6	1.7	1.3
7.0–7.9	0.6	1.3	2.2	1.2
8.0–8.9	0.9	1.3	1.0	1.0
9.0–9.9	0.9	1.0	1.0	1.0
>10.0	0.6	0.7	0.8	0.7
Average hemoglobin gain (gm./wk.)	0.9	1.2	1.2	1.1

NOTE: Figures in last column represent averages.

In thirty-nine of the patients there was repetitive menstrual blood loss during the therapeutic trial. It can be seen in Table V that the net hemoglobin gain (in gm. per 100 ml.) per week of therapy averaged 0.6 gm. per 100 ml. When the rate of regeneration was determined by initial hemoglobin and by calculated menstrual iron loss, numbers of patients in

TABLE V

Net Gain* in Hemoglobin Concentration per Week of Therapy

Blood loss (as mg. of iron)	Nil	<39	40–79	80–119	120–159	160–199	≥200	
Initial hemoglobin level (gm./100 ml.):	Net Hemoglobin Gain (gm./wk.)							
<6.0	1.7	..	..	0.7	0.5	1.0	0.9	1.2
6.0–6.9	..	0.4	0.9	0.7	..	..	0.7	0.7
7.0–7.9	1.4	0.5	..	0.6	..	0.8	0.8	0.7
8.0–8.9	0.6	0.4	0.4	0.5	0.6	..	0.7	0.5
9.0–9.9	0.4	0.3	0.5	0.6	..	0.7	0.6	0.4
>10.0	0.3	..	0.5	..	0.2	..	..	0.3
Average net hemoglobin gain (gm./wk.)	0.9	0.4	0.6	0.6	0.4	0.8	0.7	0.6

NOTE: Figures in last column represent averages.

* Gain in blood hemoglobin concentration adjusted for observed menstrual loss.

each subgroup were small. As a result, we were unable to detect any differences at the 60, 100 or 300 mg. dosage level of iron. Thus, we have combined the groups in this table. There appears to be positive correlation between the amount of hemoglobin regeneration and (1) the extent of iron loss per menses, and (2) the initial level of hemoglobin concentration. However, the effect of menses has reduced the hemoglobin regeneration by from 0.3 to 0.6 gm. per 100 ml. per week as compared to the response prior to the onset of menstruation (Table IV) during which therapeutic period no blood loss occurred.

COMMENTS

Well documented evidence[8] reveals that the average American woman has a dietary iron intake of 12 to 15 mg. per day. Of this amount, some 10 per cent (1.2 to 1.5 mg. per day) can be absorbed and utilized. Daily losses, exclusive of menses, pregnancy or lactation, amount to 1 mg. or less. Hence, she is easily able to maintain iron balance.

During pregnancy fetal and maternal demands for iron are increased, but so is the mother's ability to absorb this nutrient. Evidence indicates[10] that during the third trimester of pregnancy from 3.6 to 4.5 mg. of iron per day may be absorbed from a dietary intake of 12 to 15 mg. As a result, in the absence of complicating blood loss during pregnancy, delivery or postpartum, iron deficiency anemia does not develop in a normal pregnant woman. The usually accepted amount of menstrual blood loss is from 35 to 70 ml. per period, which is equivalent to 14 to 28 mg. of iron per menses. To meet this normal loss the woman needs an additional 0.5 to 1.0 mg. of iron per day to maintain a constant level of hemoglobin. From such reasoning one might conclude that only the woman having minimal menstrual bleeding could maintain her hemoglobin concentration. However, in most women during their normal menstrual lives progressively lower and lower hemoglobin values do not develop. Menstruating women do have lower levels than comparably aged men (by 2.0 to 2.5 mg. per 100 ml.) and prior to menarche and postmenopausally this sex differential tends to disappear. This hemoglobin concentration differential between the sexes is not dependent on dietary iron intake. Indeed, even in populations where iron intakes of 100 to 500 mg. per day occur, the differential persists.[11]

When there is repetitive excessive blood loss at the time of menses, iron deficiency anemia can and does occur. For practical purposes any non-pregnant, non-lactating woman with hypochromic microcytic anemia should be considered as an excessive bleeder until positively proved otherwise. Among women the obvious source of such an excess is meno- or metrorrhagia.

Early recognition by the physician of the amount of blood (hence iron) that a woman can lose through repetitive episodes of excessive menstrual flow is the best preventitive of iron deficiency anemia in women during their reproductive life. When the physician employs the usual means of evaluating a woman's menstrual history the actual amount of blood loss may be underestimated. If one utilizes the traditional classification of menstrual flow (slight, moderate or heavy) this will permit losses to be judged as within normal variation when the blood losses, as measured, are up to twice the 70 ml. of blood per period which is the accepted upper limit. So beware the menstruating woman with iron deficiency anemia!

As has been demonstrated previously,[12] the present study reconfirms that the response to hemopoietic therapy of a person with iron deficiency anemia is solely the result of administered iron. The addition of trace minerals and other hemopoietic agents in "shotgun" mixtures does not enhance the patient's hematologic recovery. The liver concentrate employed in this study contained a combination of several such other hemopoietics but had no demonstrable superiority. The level of iron therapy (100 mg. of elemental iron per day given in three divided doses) which produced maximal hemoglobin regeneration and hematologic remission time is but one-third the usually prescribed oral medication of 300 mg. of elemental iron (1.0 gm. of ferrous sulfate) per day. An incidental clinical observation related to this was the almost complete absence of annoying side effects to the 100 mg. dosage in

contrast to the recognized inability of some patients to tolerate the 300 mg. level.

CONCLUSIONS AND SUMMARY

Women with iron deficiency anemia as a result of chronic menstrual blood loss have been studied. The therapeutic effectiveness of three intake levels of oral iron as ferrous sulfate and in combination with a broad-spectrum hemopoietic liver concentrate has been studied by comparison of initial response and remission duration. The intake of 100 mg. per day of ferrous iron (as $FeSO_4$) suffices to produce maximal response.

The calculated amount of iron (in blood) lost at the time of menses was up to ten times the upper limit of the accepted norm.

From the present therapeutic trial, when iron was given as ferrous sulfate or iron in liver concentrate, it is apparent that (1) 60 mg. of iron per day does not provide for maximal hematologic response; (2) no detectable superiority was evident for the 300 mg. iron dose over the 100 mg. intake; (3) the addition of hemopoietic substances did not enhance the patient's response compared to iron therapy alone; (4) four weeks of 100 mg. per day of iron will raise the hemoglobin concentration above 10 gm. per 100 ml. when the initial value is as low as 5 gm. per cent.

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