

persons with chronic rheumatism, tuberculosis, alcoholism, renal disorders and hepatic disease seemed to have a lessened resistance.²⁶

2. There is no known specific chemical antidote for dinitrophenol.²⁷

3. In view of the rapidly increasing number of untoward effects of this drug, such as peripheral neuritis,²⁸ cataracts,²⁹ anemia, thrombocytopenia and purpura, as well as the convincing comprehensive report of the Council on Pharmacy and Chemistry for not accepting this drug in New and Nonofficial Remedies,³⁰ we feel that physicians should make every effort to discourage its use.

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THE PREVENTION OF HYPOCHROMIC ANEMIA IN PREGNANCY

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Within the past decade the high incidence of anemia in pregnancy has become generally appreciated. Although the work of Strauss and Castle,¹ Dieckmann and Wegner² and others has indicated that a 10 to 20 per cent lowering of the hemoglobin during pregnancy may be the result of hydremia and not represent true anemia, approximately 25 per cent of otherwise normal women are definitely anemic following parturition.³ The vast majority of such patients have anemia of the hypochromic variety,⁴ which has come to be associated with a virtual deficiency of available iron for purposes of blood regeneration within the body. Strauss and Castle,⁵ Davies and Shelley⁶ and other clinicians have shown that in pregnancy this anemia is to be associated not only with the presence of the fetus but also with gastric secretory defects and inadequate diets and usually may be completely relieved equally well during as after gestation by the administration of inorganic iron salts in suitable dosage. As a result of modern studies, the routine administration of iron to all pregnant women as a prophylactic measure has been advocated.⁷ Our purpose in this communication is to

present an adequately controlled series of observations on 200 pregnant women, 100 of whom received prophylactic iron therapy.

Several investigators have undertaken the problem of prophylaxis of anemia in pregnancy. Jerlov⁸ treated 120 moderately anemic pregnant women with iron and noted improvement in 90 per cent. Mackay⁹ observed that thirty women who had been treated with iron both during and after pregnancy had 4.8 per cent higher hemoglobin four months after confinement than a control group of twenty-nine similar women not treated. Davis and Walker¹⁰ administered six different proprietary preparations to a total of eighty-nine pregnant women. No matter what preparation was used, the treated patients showed higher average hemoglobin values than the control patients. The number of patients in each group was so limited, however, that conclusions drawn from the results were not statistically significant. Several of the proprietary remedies employed contained only traces of iron. It is doubtful whether any of the patients received an amount of iron that would be considered adequate in the treatment of hypochromic anemia. Richter and his associates¹¹ administered a proprietary mixture of equine liver extract, glycerated iron and hemoglobin to thirty-eight pregnant women. The average hemoglobin of this group of women was 5.5 per cent higher than that of an untreated group. Irving¹² administered iron, iron and copper, and whole liver to pregnant women in successive two month periods during pregnancy. His failure to consider the changes in hemoglobin that occur during such successive periods of pregnancy, as a result of plasma volume changes, unfortunately makes his data of little value.

METHODS

The 200 normal pregnant women studied presented themselves for routine care in the antepartum clinic when they were from three to seven months pregnant, the average being 162 days. On arrival, each patient was assigned a number in order. Blood for examination was withdrawn without stasis from an antecubital vein, and a careful dietary history was taken. Every woman was given a bottle containing 100 coated tablets, with instructions to take one tablet after each meal and to return the bottle and unused tablets at the next visit to the clinic. At all subsequent visits a fresh bottle of 100 tablets was given the patient. Unknown to her, the number of tablets remaining unused at each visit was counted and from these data the actual amount of medication taken was calculated. Patients who had been assigned odd numbers received tablets containing 0.2 Gm. (3 grains) of ferrous sulfate; patients with even numbers received tablets that were identical in appearance and size but contained lactose and no ferrous sulfate.¹³ Women who took less than one of the prescribed three tablets daily were excluded from the two series, as were also those in whom sepsis or hemorrhage developed, whether during gestation, parturition or the puerperium. The average daily intake of iron of the treated group was 0.5 Gm. (7½ grains) of ferrous sulfate.

At each visit and again one week after parturition, venous blood was withdrawn for examination. Hemo-

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The authors are indebted to the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, through whose cooperation this study was made possible.

From the Tufts and Harvard Medical services, Boston City Hospital, the Department of Preventive Medicine, Tufts College Medical School, and the Departments of Medicine and Tropical Medicine, Harvard Medical School.

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10. Davis, M., and Walker, E. W.: *New England J. Med.* **210**: 1315 (June 21) 1934.

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13. Smith, Kline & French, Philadelphia, kindly furnished the tablets of ferrous sulfate and the lactose tablets employed in this study.

globin determinations were performed at monthly intervals and one week after delivery by the Sahli method, with tubes so calibrated that 100 per cent was considered the equivalent of 15.6 Gm. of hemoglobin per hundred cubic centimeters of blood. Red blood cell counts were performed with pipets and counting chambers certified by the U. S. Bureau of Standards.

RESULTS

Initial Examinations.—Initial examinations of the two groups of women were made at approximately the same period of pregnancy. The average time after the last menstruation when the treated group first was observed was 160 days, and the untreated group, 164 days.

Forty-six of the women treated with iron partook of diets evaluated as average, which contained meat and vegetables, at least five times a week. Forty-eight women of the control group had similar diets. Seven of the treated women had better than average diets, as did thirteen of the control group. Forty-seven of the treated women and thirty-nine of the untreated women had had definitely poor diets. Thus it is apparent that there were no important differences in the diets of the two groups of women.

The average initial hemoglobin value of the 100 women of the control group was 75 per cent (11.7 Gm. per hundred cubic centimeters of blood) and of the

on each of the 200 women are presented in chart 2. At this time the average hemoglobin value of the 100 women who did not receive iron was 75 per cent (11.7 Gm. per hundred cubic centimeters), a figure that is in essential agreement with similar data obtained by Kühnel,¹⁴ Strauss and Castle,¹ Dieckmann and Wegner,² and Bland, Goldstein and First.³ Forty-five of these women had less than this amount of hemoglobin and twenty-four patients had less than 70 per

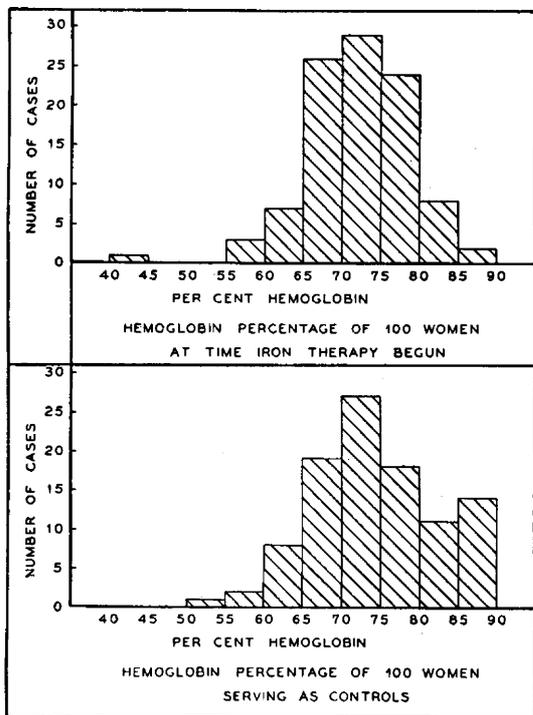


Chart 1.—Hemoglobin percentages in the sixth month of gestation.

treated group of 100 women was 73 per cent (11.2 Gm. per hundred cubic centimeters) (chart 1). The average initial red blood cell count of the control group was 3.88 million cells per cubic millimeter and of the treated group 3.72 million per cubic millimeter. There was thus no significant difference in blood levels between the two groups of women when they were first examined at approximately the beginning of the sixth month of pregnancy.

Postpartum Examinations.—The results of hemoglobin determinations performed one week post partum

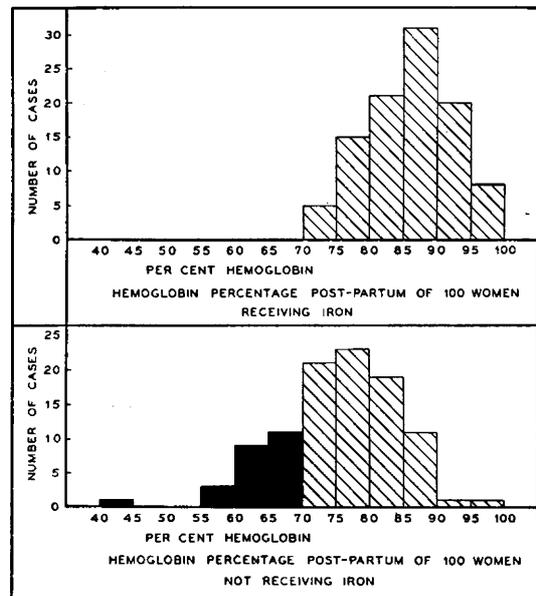


Chart 2.—Hemoglobin percentages one week post partum. Solid columns represent patients with less than 70 per cent hemoglobin.

cent (10.9 Gm. per hundred cubic centimeters) hemoglobin and hence must be considered to be distinctly anemic.

The average postpartum hemoglobin of the 100 treated women was 85 per cent (13.26 Gm. per hundred cubic centimeters), or a gain of 12 per cent over their average values in the sixth month of gestation. Only five of these 100 women had less than 75 per cent hemoglobin and none had less than 70 per cent.

The average erythrocyte count post partum in the control group was 3.94 million per cubic millimeter and in the treated group 4.28 million per cubic millimeter.

COMMENT

In 1930, evidence drawn from a study of three cases was advanced⁵ in favor of the theory that severe hypochromic anemia in pregnancy was due to a virtual deficiency of iron brought about by gastric secretory defects in the presence of fetal blood requirements. Subsequent studies¹⁵ verified this theory and led to the suggestion that iron be employed as a prophylactic of hypochromic anemia in pregnancy. The data presented here unequivocally demonstrate that, in the absence of hemorrhage or sepsis, the daily administration of 0.5 Gm. of ferrous sulfate to women in the last trimester of pregnancy results in higher hemoglobin values than in untreated women.

SUMMARY

Two hundred women were studied during the last four months of pregnancy. Alternate patients were given 0.5 Gm. of ferrous sulfate daily. The others

14. Kühnel, Paul: Ztschr. f. Geburtsh. u. Gynäk. 90: 511, 1927.
15. Strauss and Castle.¹ Davies and Shelley.⁸

received placebos. Of the 100 women given no iron, twenty-four had less than 70 per cent hemoglobin post partum. Of the 100 women given iron, none had less than 70 per cent hemoglobin post partum.

The conclusion is drawn that hypochromic anemia in pregnancy may be largely prevented by the routine administration of iron, especially in the latter months of gestation.

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Clinical Notes, Suggestions and New Instruments

RAT-BITE FEVER FROM FIELD MOUSE

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Rat-bite fever, or sodoku, is now a widely known disease. In most cases the disease is caused by the bite of rats and only rarely by the bite of other animals, such as dogs, cats or ferrets. In 1932 in Germany Jungbluth¹ reported that a boy, aged 9 years, who had been bitten by a field mouse, developed a disease which clinically resembled rat-bite fever. The demonstration of spirilla was not possible. Brüning² included this case in a compilation of sixty-five cases of sodoku in children as the only one in which the patient was not bitten by a rat. In 1932 also, Jenkinson and Jordan³ published a report from North America of the development of rat-bite fever in a man, aged 56, who was bitten by a wild mouse; the diagnosis could be made only by clinical evidence; all efforts to demonstrate the causative organism failed.

We believe that the following case, which we studied in 1934, is the first in which the bite of a field mouse produced a typical rat-bite fever in which spirilla were demonstrated as the cause:

REPORT OF CASE

History.—May 30, 1934, a previously healthy schoolboy (T. E.), aged 14, was bitten on the left fourth finger by a wild field mouse that he had captured in a California hay meadow. The wound was small, bled freely, and in a few days healed without soreness or signs of inflammation. June 11, however, there was pain and slight swelling at the site of the bite, and there was a general feeling of malaise, headache, and a loss of appetite. June 14 the finger was incised, but no pus was obtained. The patient was admitted to Mills Memorial Hospital, San Mateo, Calif., June 17.

At the time of admission, he had a temperature of 103 F., pulse 110, respirations 20. His cheeks were flushed and he exhibited sporadic muscular twitching in the muscles of his face, abdomen and extremities. There were no abnormal manifestations aside from a soft blowing localized systolic murmur over the apex of the heart; and a grayish dry crust about 0.5 cm. in diameter, at the base of the left fourth finger, surrounded by considerable cellulitis. There was no fluctuation and the tenderness was slight. There were no signs of lymphangitis. The left epitrochlear glands were painful and were moderately enlarged. Removal of the crust left an ulcer 0.5 cm. deep, which did not bleed.

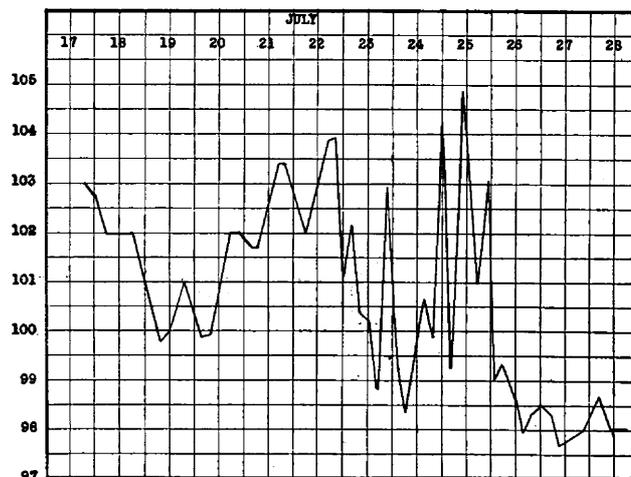
Clinical Course.—The temperature is given in the accompanying chart. Throughout the entire illness there were no subjective symptoms except headache, malaise and chills, as one would expect, with rise in temperature. June 20 the spleen was palpable for the first time 1 cm. below the costal margin. June 23 a small urticaria-like wheal was visible on the inner surface of the right thigh. The next day numerous slightly raised reddened areas, varying in diameter from 0.5 to 1 cm., appeared on the dorsal surface of the left forearm. During

the next two days, similar widely scattered lesions appeared on the lips, cheeks, chest, thighs and lower portion of the legs. At the height of their development (which was during the third to the fourth day after the initial appearance of the rash) the skin lesions appeared as discrete, purplish red, indurated nodules, not painful, tender or itching.

Medication.—June 24, 0.15 Gm. of neoarsphenamine was given intravenously. June 26, 0.3 Gm. was given; June 28, 0.15 Gm. was given. Following the second dose, the rash disappeared rapidly and the temperature fell to normal. The patient left the hospital in June and appeared entirely well until July 16, when his temperature suddenly rose to 103 F. No skin lesions were manifest but there was slight generalized adenopathy. He was given 0.15 Gm. of neoarsphenamine. The next day his temperature rose to 105 F., and 0.3 Gm. of neoarsphenamine was given. The following morning his temperature fell to normal and remained so. July 19 he was again given 0.3 Gm. of neoarsphenamine and July 24 a final dose of 0.4 Gm., at which time he was apparently well and the adenopathy had almost entirely disappeared. He had no further relapses.

Laboratory and Bacteriologic Data.—On the sixth day after entry to the hospital, the urine showed a trace of albumin and a few hyaline casts.

There was no anemia. The leukocyte count on entry was 4,400; polymorphonuclears, 67 per cent; lymphocytes, 22 per cent; monocytes, 9 per cent; basophils, 1 per cent. Daily leukocyte counts were made and the total number of cells remained



Temperature curve

low with practically the same differential count until June 26, when the white cell count rose to 7,900 with a normal differential count. The blood Wassermann reaction was negative on two occasions.

Cultures taken from the site of the wound and from the blood were repeatedly negative for pathogenic organisms. Agglutination tests for tularemia and brucellosis were negative.

Tissue fluid from the wound, which was inoculated into mice, was negative. Repeated examinations of smears of the patient's blood examined after using Wright's and Giemsa's stains were negative. Twice, citrated venous blood was inoculated into white mice and guinea-pigs intraperitoneally and into a rabbit intravenously. June 23, a lymph node was removed from the left epitrochlear region. This was ground up and inoculated into white mice and guinea-pigs. Positive results were obtained only in the mice. In one mouse (gland) the organisms were found after fourteen days and in another (blood) after sixteen days, following daily darkfield examinations of the blood taken from the tail.

The parasites showed all characteristic features of *Spirillum minus* (Carter), which is identical with *Spirochaeta morsumuris* described by the Japanese authors and generally accepted as the causative organism of rat-bite fever (sodoku). The darkfield illumination revealed the spirilla as having rigid bodies with rapidly moving bipolar flagella. The stained smears showed them to be from 2 to 5 microns in length with three to four waves.

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