IRON ENCEPHALOPATHY

BY

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The problem of refractory microcytic hypochromic anaemia has been satisfactorily solved in many cases by the intravenous administration of an iron-sucrose complex (Nissim, 1947). Nevertheless, iron by intravenous injection and even by mouth is not entirely without risk. Iron-poisoning was quite common for some years after Pierre Blaud introduced his famous pill in 1832. No further cases were reported until recent years, when, after a period of neglect, the practice of giving inorganic iron salts in large doses by mouth became established again as useful treatment for hypochromic anaemia. Recently, ferrous sulphate by mouth has caused acute gastritis and death from hepatic failure.

Cerebral symptoms following oral iron medication in man are rare. Hurst (1931) reported the case of a very anaemic woman of 58 (Hb 18%) who took 40 gr. (2.6 g.) of iron and ammonium citrate a day. On the 22nd day of treatment (her Hb having risen to 51%) she complained of severe headache and had nine convulsions within 24 hours. Between the attacks she was semi-conscious and had twitching of the right side of the face. She made a good recovery. Beyond saying that the cerebral symptoms resembled those of lead encephalopathy, Hurst gave no opinion on their mechanism, and his title "iron encephalopathy" seems hardly justified on the data published.

Napier (1936) reported a case of presumed iron encephalopathy in an Indian man aged 30 who, after receiving 468 gr. (30 g.) of ferrous sulphate in 26 days for a simple hypochlorhydric anaemia (Hb 18%), had a series of seven fits during a day. He also refers to the case of a woman who had fits following a daily dose of 12 gr. (0.8 g.) of ferrous ammonium citrate for 33 days. Whether the iron had been responsible or not seems doubtful, as the Wassermann reaction was strongly positive.

Mooney (1950) mentions intense headache following an intravenous injection of 100 mg. of saccharated iron.

In the case recorded below severe cerebral symptoms occurred after the intravenous administration of iron.

Case Report

A housewife aged 54, of average mental capacity, attended hospital on January 12, 1949, with a history of increasing dyspnoea and lassitude for three years and of oedema of the ankles and soreness of the tongue for two months. She had no dysphagia. Her menses had been heavy until September, 1947, when they ceased. There was no other history of blood loss. Her diet had been inadequate, though she had not lost weight. There had been no previous illnesses, and she had had two normal pregnancies.

On admission the patient appeared pale. There was no glossitis. The pulse was regular, the blood pressure 160/70. The heart was not enlarged. A soft systolic bruit was audible over the praecordium, but was not thought to indicate valvular disease. No abnormality was found in the lungs, abdomen, pelvis, or central nervous system.

Investigations.—Hb, 41% (6 g.); R.B.C., 3,400,000 per c.mm.; colour index, 0.6; reticulocytes less than 1%; W.B.C., 7,300 per c.mm.—differential count normal. A fractional test meal showed histamine-fast achlorhydria. A radiograph of the chest was normal. The urine was normal. A diagnosis of hypochromic microcytic (iron-deficiency) anaemia was made.

Progress and Treatment

Intravenous iron therapy was begun, using a solution of saccharated iron oxide (containing 100 mg. of iron in 10 ml.). On the assumption that each 100 mg. of iron should raise the haemoglobin by 4% the total requirement for this patient was 1,500 mg.

On January 14 and 15, respectively, 20 mg. and 50 mg. were given, the injections being made slowly into a vein in the antecubital fossa. On the 17th, after receiving 40 mg. of the iron, the patient complained of dizziness and of tingling in the hands. She also stated that everything appeared "stripy." She then vomited. The injection was discontinued. After this, injections were continued daily, none of them being greater than 75 mg. Only minor complaints of nausea and general malaise were made.

By January 23, the ninth day after the injections were started, a total dose of 380 mg. of iron had been administered. On this day the patient complained of headache and appeared to be very anxious. She later vomited twice. No injection was given. At 7.30 p.m. the nursing staff noted that she seemed strange in her manner and somewhat drowsy. At 9.30 p.m. she had a convulsion, after which she remained deeply unconscious. Her limbs were flaccid and her eyes deviated to the right. Her pulse rate was 120 a minute and the rhythm irregular. There was no pulse deficit. Further convulsions then occurred at intervals of about 20 minutes. Each of these began in the left hand and spread to include the left side of the face, the left leg, and finally became generalized. The C.S.F. pressure was 230 mm., and routine laboratory examinations showed no abnormality. The Wassermann reaction was negative in both the C.S.F. and the blood. Large doses of paraldehyde (16 ml. in all) were given intramuscularly, but the convulsions became more frequent until at 1 a.m. on January 24 they were recurring at five-minute intervals. Thereafter they became less frequent and were confined to the left side of the body. They finally ceased at 4 a.m.

The patient remained unconscious during the next 12 hours, but responded to pinching by groaning or by moving one or other leg. Many minute petechiae were visible over the chest and arms, and bruising had occurred at the sites of pinching. A mild left hemiplegia, affecting the arm more than the leg, was present: this gradually improved during the next three days. Her bleeding-time was 40 seconds; and the clotting-time five minutes; platelets numbered 135,000 per c.mm.; the capillary resistance test (Rumpel-Leede) was positive; and the urine was normal.

By January 28 the patient was conscious and rational. She was able to write and to read a few words correctly, but unable to understand what she read. At 5.45 p.m. she suddenly lapsed into a dreamy state. She sat up in bed and appeared to be completely detached from her surroundings, making no response to the spoken word or to painful stimuli. The few words she uttered (which often included "green" and "yellow") indicated a gross dysphasia. Although this speech defect was associated with a left hemiparesis, she was not left-handed. The only other sign of note was the presence of spontaneous nystagmus. This dreamy state lasted for 36 hours.

By March 8 she was able to read accurately, but a tendency, previously noticed, to read only the right half of printed lines persisted. Her visual fields were apparently full, but co-operation was poor. Her general condition was good, and she was able to walk with assistance. She complained intermittently of occipital headache. The

haematological response to the iron was excellent. There had been a good reticulocytosis, and the haemoglobin rose steadily to 82% (12.1 g.%) on February 2.

She was discharged from hospital on April 1 and returned as an out-patient on April 30. Her haemoglobin was then 92% (13.6 g.%). There were no abnormal physical findings, but she still complained of headache. She was very anxious, and she easily "paricked." Though able to carry out simple household duties, she could not cook a full meal or do any shopping, and was quite unable to make any calculation or to count change. She has remained more or less in the same condition ever since, but has become increasingly depressed at the persistence of her disability, of which she seems fully aware. Her haemoglobin level on June 1, 1950, was 106%.

When last seen on June 24, 1950, she was a little unsteady on her feet. She was depressed at times and tended to be muddled over money. These symptoms were less marked than they were originally. An electroencephalogram at this time showed evidence of bilateral damage in the temporo-parietal regions.

Discussion

Two well-known proprietary preparations have been used many times in other cases without serious mishap. On this occasion both were out of stock, and ampoules of a privately made preparation were offered instead by the pharmacist and accepted for use. It was not fully realized by all concerned that this preparation was other than had been safely used before. It was a solution of saccharated iron oxide prepared from ferri oxid. sacch. equivalent to 100 mg. of elemental iron (Fe) and "apyrogen" (pyrogen-free distilled water) to 10 ml. The saccharated iron oxide was dissolved in the apyrogen with the aid of heat, and the solution was filtered through filter paper while still hot. It was filled into ampoules and autoclaved at a pressure of 10 lb. per sq. in. (0.7 kg. per cm.²) for half an hour. Subsequent analysis of the preparation showed that it contained the correct amount of elemental iron (Fe) and 21.6% of sucrose, the pH being 8.7.

Compatibility with serum *in vitro* was demonstrated by mixing 2 ml. of the solution with 2 ml. of normal horse serum, and 0.1 ml. of the solution with 5 ml. of normal horse serum. These mixtures were incubated at 37° C. for one hour and gave no macroscopic or microscopical evidence of coagulation or precipitation. Similar tests with the patient's serum and that of normal human controls were negative. It must not be assumed, however, that precipitation would not occur *in vivo*, and Nissim and Robson (1949) found evidence in mice that a gradual precipitation of proteins did occur *in vivo* and suggested that the compound was broken down gradually as the sugar part of it was metabolized. The LD50 of the sample administered intravenously to mice was approximately 118 mg. per kg., whereas the most suitable preparations were found by Nissim and Robson (1949) to have an LD50 of 300 mg. per kg.

The available evidence does not satisfactorily explain the production of cerebral symptoms. The importance of using pure chemicals in making saccharated iron oxide is emphasized by Robson and Keele (1950), who point out that some of the more transient reactions can be avoided by using analytical grade reagents—for example, "analar" sucrose. Somers (1947) showed that very large doses of iron preparations given by mouth would kill animals, resulting in convulsions and coma for which no adequate organic basis could be found. Cappell (1930) studied the fate of intravenous

injections of colloidal solutions of saccharated iron oxide in mice and rats. They did not cause flocculation in contact with plasma, and so pulmonary embolism did not occur. The iron was taken up by the cells of the reticulo-endothelial system, and later formed a loosely bound compound with plasma proteins, through which it was distributed to other organs, notably the liver. Some iron was deposited in the walls of the brain capillaries, but it was rapidly removed, and thereafter no iron was found in the nervous tissues. It is conceivable, however, that capillary damage, sufficient to lead to subsequent injury to the brain, might be caused by some iron preparations.

Polson (1928), in attempting to produce haemochromatosis in rabbits by injecting dialysed iron intravenously, found that pulmonary embolism, presumably from flocculation, was easily caused by long or rapid injections. Ledofsky (1924) injected a 33% solution of saccharated iron several times into eight moribund patients, but no iron could be demonstrated in the brain tissue histologically. Goetsch *et al.* (1946) attributed the toxic effects of iron to a "heavy metal effect," but this term is usually understood to mean the formation of a metallic proteinate when a soluble metallic salt is mixed with a solution of protein. We know that in the present case the preparation used did not produce a proteinate with the patient's plasma.

The analogy of "lead encephalopathy" is not helpful, since the pathology of this state is unknown apart from the findings of arteriosclerosis and meningeal fibrosis in chronic cases.

Summary and Conclusions

A case is reported of severe cerebral symptoms in a woman aged 54 after the intravenous administration of 380 mg. of iron in nine days. The symptoms are tentatively ascribed to iron encephalopathy, but the mechanism of their production remains in doubt. The use of certain proprietary preparations of iron for intravenous use is known to be valuable and fairly free from toxic effects if these preparations have an LD50 for mice of 300 mg. or more per kg. and if dosage is kept below 100 mg. of iron a day. The danger of using unproved preparations is emphasized.

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On May 31, 1950, the Royal College of Obstetricians and Gynaecologists comprised 837 Members and 322 Fellows. Seventy-three of the Fellows belonged to the London division, and Liverpool and Manchester together contained 20, the greatest concentration outside London. Out of 31 Scottish Fellows, Edinburgh contained 11 and Glasgow 14; in Ireland, 9 were in Belfast and 13 in Dublin; while Melbourne and Sydney (Australia) and Montreal (Canada) had 10 Fellows each.