wood, 1958 ; Webster *et al.*, 1959). The occurrence of the electrolyte changes may merely be a reflection of the severity of the disease and its duration. It is probable that our case was diagnosed very early in relation to the onset of the adrenal overactivity, and had the patient lived long enough it is likely that she might have developed the electrolyte changes. Her death was due to tracheal compression by the neoplasm and not to adrenal overactivity as is usual in these cases. The early or mild case may well escape detection, and in our case the diagnosis was made only by doing the right investigation for the wrong reason. It may well be that what we believe to be the typical case of this disease is in fact the late severe case, the milder earlier cases being missed.

Summary

A case of Cushing's syndrome associated with a carcinoma of the bronchus is described. The unusual features were the complete absence of physical signs of Cushing's syndrome and the presence of normal plasma electrolytes. It is suggested that this may have been a very early example of this disease, which may be missed because of lack of clinical or biochemical abnormalities that would direct attention to more detailed investigation of the adrenal gland. Alternatively, the hyperplastic adrenal may be producing an 11-hydroxycorticosteroid other than cortisol, determined by our method for plasma cortisol and excreted in the urine as the usual breakdown products.

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References

Allott, E. N., and Skelton, M. O. (1960). *Lancet*, **2**, 278.
Bagshawe, K. D. (1960). Ibid., **2**, 284.
Bayliss, R. I. S. (1957). *Proc. roy. Soc. Med.*, **50**, 761.
Billinghurst, J. R., Thould, A. K., Galpin, O. P., and Hinton, J. M. (1961). *Brit. med. J.*, **2**, 490.
Brown, W. H. (1928). *Lancet*, **2**, 1022.
Holub, D. A., and Katz, F. H. (1961). *Clin. Res. Proc.*, **9**, 194.
Lockwood, C. H. (1958). *Canad. med. Ass. J.*, **79**, 728.
MacPhee, I. W. (1959). *Brit. J. Surg.*, **46**, 456.
Mason, A. S., Richardson, J. E., and King, C. E. (1958). *Lancet*, **2**, 649.
Mattingly, D. (1962). *J. clin. Path.*, **15**, 374.
Meador, C. K., Liddle, G. W., Island, D. P., Nicholson, W. E., Lucas, C. P., Nuckton, J. G., and Luetscher, J. A. (1962). *J. clin. Endocr.*, **22**, 693.
Rosenthal, F. D. (1957). *Brit. med. J.*, **2**, 139.
Scholz, D. A., Riggs, B. L., Bahn, R. C., and Liddle, G. W. (1963). *Proc. Mayo Clin.*, **38**, 45.
Soffer, L. J., Eisenberg, J., Iannaccone, A., and Gabrilove, J. L. (1955). In *Ciba Foundation Colloquia on Endocrinology*, edited by G. E. W. Wolstenholme and M. P. Cameron, vol. 8, p. 487. Churchill, London.
Thorne, M. G. (1952). *Guy's Hosp. Rep.*, **101**, 251.
Webster, G. D., jun., Touchstone, J. C., and Suzuki, M. (1959). *J. clin. Endocr.*, **19**, 967.

Reactions to Total Dose Intravenous Infusion of Iron Dextran (Imferon)

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Iron-deficiency anaemia is still the most common problem encountered during pregnancy, especially among women of the lower social classes. It occurs frequently in Hull, where over a five-month period selected patients were given parenteral iron by the " total dose infusion " method discussed below.

Antenatal treatment is aimed at achieving a haemoglobin level of at least 80% (Haldane) before term (Davidson, 1957 ; Giles and Burton, 1960). Oral iron is routinely prescribed at the antenatal clinics, and is eminently satisfactory provided the patient can tolerate it and remembers to take it.

Parenteral iron has the advantage that it is seen to be given and the dose is therefore known. Intramuscular iron, however, has the disadvantages of staining, which may occur despite the careful use of a " Z "-shaped injection route, and intramuscular iron dextran (Imferon) has been questioned with regard to potential carcinogenic properties (Richmond, 1959). Intravenous saccharated iron oxide (Ferrivenin) shares with intramuscular preparations the disadvantage of repeated injections, and has been reported to have a 5% reaction rate (Laurence and Moulton, 1960).

More recently, the stability of the iron–dextran complex when dissolved in 5% dextrose has been noted and the possibility of a single infusion of a large quantity of iron in high dilution completely correcting the patient's iron deficit has been welcomed.

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Method

The method involves calculation of the required dose from the manufacturer's tables, correlating the initial haemoglobin and the patient's weight, to a maximum of 2 g., and dissolving it in 5% dextrose, using a sterile technique, so that the solution is not more than 4% v/v. Scrupulous care must be taken to avoid traces of alcohol, detergents, or strong electrolytes contaminating the solution, the giving set, or the site of venepuncture. The infusion is begun at 15 to 20 drops per minute for the first half-hour ; this constitutes the " test dose." The drip is then run at 40 d.p.m. for the remainder of the infusion. As a precaution, all other iron therapy is discontinued for 24 hours prior to treatment by this method.

Over the period of five months, from 1 July 1963, 150 patients were treated in this way at Hull Maternity Hospital. Haematological reports indicated " hypochromic anaemia " with a haemoglobin level of 66% (Haldane) or less, and no improvement occurred after three weeks on " double oral iron "—that is, ferrous sulphate or ferrous gluconate tabs. 2 t.d.s. All the patients except 22 post-natal cases were in the last trimester of pregnancy, and most were within four to six weeks of term. All had been given oral iron, and the majority said they had taken it.

Of the 150 patients treated, 103 had infusions of 1.5–2 g. of Imferon in 3%–4% solution ; five had infusions of 1–1.5 g. (2%–3% solution), and 42 had infusions of 1 g. (2% solution).

The haemoglobin levels were checked subsequently at the clinic, and by four weeks after treatment very few patients were not showing improvement (see Table).

Percentage (Haldane) Haemoglobin Improvement Measured in 117 Patients 4–6 Weeks After Infusion

Hb % rise	<5	5–	10–	15–	20+
No. of patients ..	10	69	28	6	4

Reactions

Thirteen reactions were classified as moderate or severe. Moderate reactions were those accompanied by such general symptoms as nausea, vomiting, faintness, "ringing in the ears," and in one patient a feeling of stiffness in the arms and neck. Signs observed included flushing, pallor, and clamminess of the hands. Such reactions occurred in six patients. In all these cases the patient was reassured by the doctor who was present, and all were successfully talked out of their "reactions." All completed their infusions without further incident.

We classified as severe those cases which required resuscitative treatment. These numbered seven, and all are described. All had been questioned for any past history of allergic manifestations and gave none. No reactions occurred in the 22 post-natal cases.

Severe Reactions

Case 1.—A gravida-3, aged 25, 37 weeks pregnant, Hb 66%, began an infusion of iron dextran 2 g./l. 5% dextrose, following the usual routine. After only two or three drops had been run she became pale, and her pulse and blood-pressure were not recordable. The infusion was immediately discontinued, the foot of the bed blocked, oxygen given by mask, and Piriton (chlorpheniramine hydrogen maleate) 10 mg. intravenously. The pulse returned and the blood-pressure was 80/40. She still looked ill and intravenous hydrocortisone 100 mg. was followed by a noradrenaline drip. The blood-pressure rose to 150/80, pulse 100. She was observed closely and her condition gradually improved over the next hour and a half. She was discharged next day on oral iron, and three weeks later, having had no further untoward effects, she had a normal delivery of a healthy female infant, weighing 7 lb. 4 oz. (3,290 g.). Six weeks post partum her haemoglobin was 86%.

Case 2.—A gravida-3, aged 24, 37 weeks pregnant, Hb 65%, was admitted for Imferon 2 g. Five minutes after starting the infusion she complained of difficulty in breathing and became cyanosed. After cessation of the drip, oxygen, subcutaneous adrenaline, intravenous Piriton 50 mg., and hydrocortisone 100 mg. were needed before she improved. She went home next day taking oral iron, and four weeks later was delivered normally of a healthy female child weighing 7 lb. 11 oz. (3,485 g.). After delivery her haemoglobin was 73%.

Case 3.—A gravida-2, aged 18, 36 weeks pregnant, Hb 60%, was admitted for Imferon 2 g. Almost immediately after starting the infusion she had a severe reaction, with dyspnoea, cyanosis, and facial oedema. The drip was discontinued and she was revived with oxygen, subcutaneous adrenaline, and intravenous hydrocortisone. She recovered in a few minutes and went home taking oral iron. Four weeks later she had a normal delivery of a healthy female infant weighing 8 lb. 6 oz. (3,800 kg.). Her haemoglobin after delivery was 86%.

Case 4.—A gravida-1, aged 20, 38 weeks pregnant, Hb 66%, was admitted for 2 g. Imferon. Almost immediately after this was begun her face became red and she developed a fine urticarial rash on the face and neck. She complained of difficulty in breathing. The drip was stopped and she recovered after Piriton 10 mg. intravenously. She was discharged home on oral iron and folic acid 5 mg. t.d.s. Three weeks later she was delivered normally of a healthy female child of 7 lb. 5 oz. (3,315 g.) After delivery her haemoglobin was 69%, and she went home taking oral iron. Unfortunately she did not attend the post-natal clinic, so her further progress is not known.

After these four cases of reaction it was decided to precede infusions by giving Piriton 10 mg. intravenously. Despite this precaution two further reactions occurred.

Case 5.—A gravida-8, aged 27, 38 weeks pregnant, Hb 60%, was admitted for 2 g. Imferon. When the drip had been running for two minutes she complained of a choking sensation, began to cough, and became cyanosed. Her pulse became very thready; the blood-pressure was not then recorded, but, the drip having been stopped at once, she was given oxygen and intravenous hydrocortisone 100 mg. She rapidly improved with an increasing pulse volume, the rate returning to 90/min. She went home the next day and had no untoward effects from the course of intramuscular iron then given by her general practitioner. Four weeks later she had a normal delivery of a healthy female child weighing 6 lb. 9 oz. (2,975 g.). After delivery her haemoglobin was 69%.

Case 6.—A gravida-2, aged 22, 32 weeks pregnant, Hb 64%, was admitted for 2 g. Imferon. She was known to have a multiple pregnancy. After only a few drops of the infusion had been given she complained of feeling hot, but said, "I often do with a needle." Her pulse was unchanged and her colour good, so the drip was continued after a few minutes, when she said she felt all right. She then started coughing, developing spasm, and became cyanosed and unconscious despite immediate cessation of the drip. She was given subcutaneous adrenaline, and after two minutes her colour and respiration returned to normal. The next day she was discharged home on oral iron and folic acid. No further untoward incidents occurred, and six weeks later she was delivered of healthy female twins weighing 4 lb. 11 oz. and 5 lb. 2 oz. (2,125 g. and 2,325 g.). After delivery her haemoglobin was 75%.

After these two further reactions it was decided that we should reduce the concentration of the solution; accordingly 42 patients were treated with drips of no more than 2% Imferon. The following severe reaction occurred.

Case 7.—A gravida-1, aged 18, 36 weeks pregnant, Hb 59%, was admitted for Imferon 1 g. After one minute of the infusion she became cyanosed and had oedema of the face and eyelids. She also coughed and vomited, and complained of abdominal pain. Her pulse was 120/min. and B.P. 120/70. She was treated with Piriton 10 mg. intravenously, followed by hydrocortisone 100 mg. and improved within a few minutes. She went home the next day feeling quite well, and was given intramuscular iron by her general practitioner without ill effect; she also took folic acid tablets. She was later readmitted to the hospital for induction of labour on account of estimated post-maturity of 14 days. This was done by low amniotomy, and she was successfully delivered of a healthy female infant of 7 lb. 11 oz. (3,485 g.). After delivery her haemoglobin was 70%.

Discussion

In 150 cases seen at Hull Maternity Hospital over a five-month period, it was felt necessary to give parenteral iron, and the total-dose-infusion technique was used. Previous authors have emphasized the safety of the method: Basu (1963) described "no untoward reaction," and Lane (1963) "one reaction in 30 cases." We were impressed by the described satisfactory response to the treatment, and in the large majority of cases our results confirmed this. However, at the end of the five months it was felt that in view of the number of severe reactions we experienced, despite all precautions, this form of treatment was no longer to be regarded as justifiable. The previous reports of the safety of the method made us suspect our technique rather than the drug. Why should the findings in Hull have been so different?

After their experiences with the intravenous infusions, the patients seem to have remembered their oral iron, for all five who had had it achieved an improved haemoglobin level. The importance of the drug was more than usually stressed to them at every opportunity.

The second point of interest is that all the babies of the patients with these severe reactions were females; this includes the pair of twins. Thirdly, no reactions occurred among the post-natal patients.

Conclusions

We have noted no other similarities in our cases, but the manufacturers have been searching for some cause. The possibility of some reagent used in the sterilization of the syringes causing instability of the iron dextran complex has been suggested, but seems unlikely. However, until the problem can be solved, this method of iron therapy has been suspended. It certainly has many advantages, but we have noted that oral iron, with sufficient coercion of the patient, will give satisfactory haemoglobin levels in the great majority; the remainder appear to be those who have a folic-acid deficiency in addition to their iron deficiency.

Summary

One hundred and fifty maternity patients were treated with intravenous Imferon by the total-dose-infusion technique. Thirteen reactions occurred, of which seven were severe and demanded emergency treatment. All those who suffered reactions were later safely delivered of healthy infants. All the babies were girls. No reactions occurred in any of 22 postnatal patients treated. In view of the reactions, treatment by this method was suspended. We were unable to discover the cause for the reactions.

This account is published in order to point out that, despite the reported safety of this method, such was not our experience.

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NOTE.—Since this article was written the manufacturers have sent an undated letter to members of the profession reporting the death of a diabetic patient attributed to this technique. Further, in view of the occasional occurrence of thrombophlebitis, it is now recommended that Imferon be dissolved in normal saline.

REFERENCES

Basu, S. K. (1963). *Lancet*, **1**, 1430.
Davidson, W. M. (1957). *Practitioner*, **178**, 161.
Giles, C., and Burton, H. (1960). *Brit. med. J.*, **2**, 636.
Golberg, L. (1959). In *Iron in Clinical Medicine*, edited by R. O. Wallerstein and S. R. Mettier. Cambridge, London.
Lane, R. S. (1963). *Lancet*, **2**, 1015.
Laurence, D. R., and Moulton, R. (1960). *Clinical Pharmacology*, Ch. 24, 388. Churchill, London.
Richmond, H. G. (1959). *Brit. med. J.*, **1**, 947.

Preliminary Communications

Effect of Intrauterine Silk Thread Suture on Fertility of Female Rats

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A plastic intrauterine loop is being investigated as an antifertility agent, and studies are being carried out in humans. This method of fertility control, which appears to be cheap and efficient, can finally be accepted only after its mechanism of action and possible toxic effects have been thoroughly investigated in experimental animals. The presence of a loop in the uterine horn of the female rat also interferes with pregnancy, and this is a situation similar to that observed in humans (Doyle and Margolis, 1963). We have investigated the effect of an intrauterine silk thread suture in the lumen of one and both horns of the uterus on (*a*) pregnancy, (*b*) the gonadotrophin content of the pituitary, (*c*) the oestrous cycle, (*d*) lactation, (*e*) teratogenicity of the litter born when there is a suture in one horn, and (*f*) sperm migration in the uterine horn with the suture. The effect of removal of the suture on later pregnancy has also been studied.

EXPERIMENTAL

Sixty female rats were operated upon under ether anaesthesia, and a silk thread was inserted in 30 rats in one horn of the uterus. The suture was introduced through the muscular layers into the lumen of the horn, down which it ran for about 4 mm. The thread was then brought to the surface of the horn again and anchored by knots at each end. Twenty of these rats were sacrificed on the 14th day and 10 were allowed to go to term. In 30 rats the silk thread suture was placed bilaterally into the lumen of both horns of the uterus. Twenty of these rats were also sacrificed on the 14th day and 10 were allowed to go to term. In 20 animals a sham operation was performed in that the rats were operated on under ether anaesthesia and the silk thread suture was inserted bilaterally in both horns and immediately removed. The sutures in all experiments were placed longitudinally and did not block the patency of the tube. After a week the oestrous cycle of the rats was studied and they were mated with males of proved fertility. Pregnancy was detected by the presence of spermatozoa, and only those animals with thick masses of spermatozoa in the vaginal smear were used. Our experience in earlier antifertility studies in over a thousand rat matings leads us to believe that 98% of the rats that show masses of spermatozoa in the oestrous smear after being mated with proved males go on to successful pregnancy.

The rats were allowed to proceed to term or were killed on the 14th day and the uteri were examined to show whether implantation had occurred or not. The loop was removed under anaesthesia in 10 experiments, and after a further period of rest of 15 days the rats were mated again. A bilateral intrauterine suture was placed in 10 rats with normal cycles and a unilateral suture in another 10 to study the effect of the suture on the oestrous cycle. Sperm migration was studied in 20 female rats with unilateral sutures when the presence of sperm was detected microscopically in both horns to see if there was any difference in the rate of upward migration of the sperm.

RESULTS

Effect on Pregnancy.—When there was a suture within one uterine horn implantation did not occur on that side in any of the 20 animals, but there were normal living implants in the contralateral horn. When 10 animals with a similar suture were allowed to go to term they produced a normal litter but with fewer young, the average number being four. On examining the uterus it was observed that all the foetuses were from the side in which there was no suture. When both horns had uterine sutures there were no implants on either side in the 20 rats that were sacrificed on the 14th day, and when 10 such