Summary

The investigation has established that a consignment of endrin dispatched on February 20, 1956, leaked 3 gallons (13.6 litres) into the conveying wagon in transit. The same wagon, which was used for the conveyance of empties between February 20 and April 25, was on the latter date loaded with sacks of flour at Cardiff and dispatched to Swansea. Of the 100 sacks carried in the wagon it was proved that two absorbed endrin from the vehicle floor, and both these sacks were delivered to one bakery as part of the weekly consignment. One of these sacks was returned, and endrin was found to be present in some parts of the flour to the extent of 5,500 parts per million. The other sack was used by the baker to manufacture loaves which caused 49 people to be ill enough to require medical treatment. Endrin was recovered from some parts of the bread consumed to the extent of 150 parts per million. It was further established that while in the bakery the empty contaminated sack which had contained national flour came into contact with dough made from patent white flour which, having been used to make white bread rolls, caused 10 men to become ill at a local works after consuming them.

Samples taken from the wagon floor and analysed on June 8 showed endrin still to be present in one section of the wagon to the extent of 116,000 parts per million.

The successful result of the inquiry would not have been achieved had the public health department not received the fullest assistance and co-operation from all the firms and organizations involved. It is desired to acknowledge the assistance provided by the Department of the Government Chemist, London, and the Glamorgan County Public Health Laboratory. The information on case histories was readily provided by Dr. Duncan Davies, medical superintendent, Morriston Hospital; Dr. Idwal Pugh, medical superintendent, Hill House Isolation Hospital, Swansea; and Mr. B. J. Baker, department of electroencephalography, Morriston Hospital.

REFERENCES

- Cole, Leyland L. W. (1955). *World Crops*, 7, No. 4, p. 154.
Princi, F. (1952). "Human Toxicity of Certain Chlorinated Hydrocarbon Insecticides." Paper presented to 3rd International Congress of Phytopharmacy, Paris, September, 1952.
Spiotta, E. J. (1951). *A.M.A. Arch. industr. Hyg.*, 4, 560.

TREATMENT OF MEGALOBlastic ANAEMIA OF PREGNANCY AND THE PUERPERIUM WITH VITAMIN B₁₂

BY

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Early reports from temperate climates indicated that treatment of megaloblastic anaemia of pregnancy and the puerperium with vitamin B₁₂ was usually ineffective (Bethell *et al.*, 1948; Day *et al.*, 1949; Furman *et al.*, 1950; Ginsberg *et al.*, 1950; Ungley and Thompson, 1950; Clark, 1952). Total dosage did not exceed 120 µg. in the cases described. Later, however, a case was treated successfully in Holland with only 45 µg. (Nieweg, 1952), and recently in Dublin satisfactory responses followed the use of massive doses ranging from 900 to 5,000 µg. in 13 patients out of a series of 17 (Moore *et al.*, 1955). In warmer climates response to vitamin B₁₂ in small amounts was often satisfactory (Patel and Kocher, 1950; Chaudhuri, 1951), and good results sometimes followed the use of larger doses (Cohen, 1953; Adams and Wilmot, 1953; Tasker, 1954; Berry 1955).

Kothari and Bhende (1949) believed that the disease commonly seen in India and the Tropics was the same as that described in Britain by Callender (1944). Diagnosis depended on the presence of megaloblasts of Ehrlich in the peripheral blood or bone marrow. Cases reported from most parts of the world usually responded well to treatment with folic acid, and there were clinical similarities. Differences in response to vitamin B₁₂, however, supported the views of Thompson and Ungley (1951) and others that there are several varieties of the condition, while the work of Foy *et al.* (1952a, 1952b) in East Africa showed differences in the appearance of the bone marrow.

This paper records the results of a clinical trial using large doses of vitamin B₁₂ in 10 cases of the type of megaloblastic anaemia associated with pregnancy or the puerperium seen in Durban. The appearance of the bone marrow is briefly described.

Clinical Features

From a series of 34 patients with severe megaloblastic anaemia associated with pregnancy or the puerperium, 10 who were not dangerously ill were chosen for the trial. Two patients were African and eight Indian. Their ages and parity are indicated in Table I, which also shows the main findings in the blood on admission to hospital, and the results of gastric analysis after stimulation with histamine. Clinical features were similar to those previously described in our cases (Adams and Wilmot, 1953). These will not be discussed further except as regards infections and other factors which might be expected to retard recovery after treatment. Pyrexia was present in seven patients, all of whom were investigated for sources of infection. There was mild pyelitis in two (Cases 2 and 6); two others had com-

TABLE I

Case No.	Age	Previous Pregnancies	Haemoglobin (g./100 ml.)	M.C.V. (Cubic µ)	M.C.H.C. (%)	Reticulocytes (%)	Serum Proteins (g./100 ml.)		Serum Bilirubin (mg./100 ml.)	Free Acid
							Total	Albu-min		
1	29	5	3.9	89	25	0.5	8.1	4.8	0.8	++
2	26	1	3.2	98	26	1.2	7.0	4.0	0.4	++
3	20	0	3.1	96	36	1.6	7.3	3.4	0.6	++
4	28	10	5.6	106	27	4.4	7.9	3.4	0.2	++
5	35	5	3.2	125	32	3.3	6.0	2.6	0.9	++
6	26	0	4.4	144	35	5.4	6.6	3.5	0.8	++
7	43	7	6.9	93	33	2.3	6.0	3.2	0.8	++
8	33	8	4.4	97	35	1.3	5.8	2.5	0.8	++
9	20	0	6.5	111	34	1.4	4.7	2.3	0.7	++
10	30	9	4.4	135	33	5.9	5.6	2.5	0.4	++

plained of diarrhoea before admission, but no cause was found on stool examination. X-ray examination of the chest in nine patients revealed no abnormality. One patient had evidence of puerperal sepsis, which was not severe (Case 9), but pyrexia persisted after this had been cleared up. Full investigations revealed no cause, other than severe anaemia for this pyrexia, which settled when the blood count rose. In their series Badenoch *et al.* (1955) record a high incidence of other complications such as vomiting and haemorrhage, but these were absent from my cases. In the whole series of 34 cases there was no clinical evidence of steatorrhoea, an uncommon disease in South Africa; faecal fats estimated in 21 (six of the present trial series), were always within the normal range. It thus seems unlikely that infections or other factors have obscured the results of treatment in this trial.

Diet

Dietary histories are difficult to obtain and are not very reliable. Family incomes of all were low, and carbohydrate intake tended to be high. Protein was very low in seven, and apparently adequate in one (Case 6). One patient is of particular interest in view of the suggestion of Badenoch

and his colleagues that resistance to haemopoietic factors may develop during pregnancy.

Case 4.—An Indian woman had been under my care during the seventh and eighth months of pregnancy for severe chorea gravidarum. As she was thin she had received soured milk and an egg daily in addition to hospital diet. On admission haemoglobin was 8.6 g. per 100 ml., mean corpuscular haemoglobin concentration 29%, sedimentation rate 51 mm. in one hour (Wintrobe). Treatment consisted of bed rest, salicylates, sedation with barbiturates, and ferrous sulphate. The bone marrow was not examined. Leaving hospital against advice, she delivered a stillborn infant at home two weeks later. Severe chorea recurred immediately and she was readmitted. Examination of the blood and bone marrow revealed the presence of megaloblastic anaemia, haemoglobin being 5.6 g. per 100 ml.

Bone Marrow

Diagnosis depended on examination of the bone marrow in all cases. My experience has been somewhat similar to that of Foy *et al.* (1952a), who described two groups of macrocytic or normocytic anaemia in East Africa. In one there are giant metamyelocytes in the bone marrow with erythroblasts, macronormoblasts, and megaloblasts in various stages of development; in the other, giant metamyelocytes are present without megaloblasts. I have observed similar bone-marrow changes in some cases of kwashiorkor (Adams, 1954), and Berry describes them as a feature of some of the cases of anaemia of pregnancy in Lagos. Giant metamyelocytes were seen in all 10 of the present series, while in six there were megaloblasts of Ehrlich as well as cells of intermediate type similar to those described by Dacie and White (1949). Intermediate cells were present in the remaining four, but megaloblasts were not observed (Cases 5, 7, 8, and 10). Differentiation from true megaloblasts is sometimes difficult. For the purposes of this trial a bone marrow was reported as megaloblastic if it contained true megaloblasts or intermediate cells as well as giant metamyelocytes.

Clinical Trial with Vitamin B₁₂

Before treatment with vitamin B₁₂ was started, all cases were observed over a control period—four days in Case 6, and five to seven days in the remainder. During this control period and throughout the trial which followed, progress was determined by daily reticulocyte counts, and by haemoglobin (Hb) and the volume of packed cells (P.C.V.), both estimated in duplicate every five days. Seven patients

had previously received no treatment and two had been treated with penicillin because of pyrexia (Cases 2 and 7). Significant blood changes did not occur in any of these during the control periods. Case 5 had been treated with penicillin and streptomycin seven days before vitamin B₁₂ was given. During this time a slight rise occurred in P.C.V., while the reticulocytes rose to 12.1% but dropped again to their previous level. No change occurred in the Hb, however, and examination of the bone marrow at the end of the control period showed well-marked megaloblastic erythropoiesis. She was therefore included in the series.

Vitamin B₁₂ was administered by the intramuscular route in doses ranging from 100 µg., given in one injection, to 1,400 µg. in daily injections of 100 µg. The results are analysed in Table II, which also shows the subsequent course of each patient.

It will be seen that seven responded to vitamin B₁₂. Response was good in six, but only moderate in the seventh. In four of these the bone marrow was re-examined during the trial, and in all erythropoiesis was then normoblastic, although in one some giant metamyelocytes were still present (Case 5). Three of these patients received only 100 µg. during the trial. As a group, response appeared to be as good as that of the other four who were given 1,000 µg. of vitamin B₁₂ or more. After the trial two received folic acid (10 mg. thrice daily); there was no second reticulocytosis in one of them on whom repeated reticulocyte counts were done. Three patients later showed signs of iron deficiency, for which ferrous sulphate was given.

Vitamin B₁₂ was judged to be ineffective in two patients (Cases 8 and 10). A false reticulocytosis of 20.9% occurred in Case 8, but the Hb failed to rise in both, while the bone marrow remained megaloblastic (examined on the fifteenth and seventh days respectively). The trial in Case 9 was inconclusive. Hb and P.C.V. dropped considerably and there was no rise in reticulocytes after five days, so folic acid therapy was started; but on this day partial change in erythropoiesis was observed in the bone marrow.

Discussion

In this small series satisfactory responses followed treatment with vitamin B₁₂ in all seven cases seen after delivery, 100 µg. apparently being as effective as larger doses. There was an average daily Hb rise during the trial of 0.16 g. per 100 ml. Better response followed treatment with folic acid in 14 other post-partum cases (mean daily Hb rise 0.23 g. per

TABLE II.—Analysis of Results

Case No.	Diagnosis of Anaemia	Vitamin B ₁₂ Dosage (µg.)	Hb Before Treatment (g./100 ml.)	Response to Treatment	Subsequent Course	Result of Vitamin B ₁₂ Trial
1	14 weeks post partum	1,000 (100 × 10)	4.3	13.5% reticulocytosis on 5th day, Hb 5.9 g./100 ml. on 10th day; bone marrow then normoblastic	Slow rise on further B ₁₂ , folic acid, and iron to 12.5 g. Hb/100 ml.	Good
2	8 weeks post partum	100	3.3	34.3% reticulocytosis on 5th day; Hb 5.4 g./100 ml. on 15th day	Continued rise on further B ₁₂ and later iron to 11.6 g. Hb/100 ml.	„
3	2 weeks post partum	100	3.2	28.3% reticulocytosis on 6th day; Hb 5.4 g./100 ml. on 15th day	Continued rise on further B ₁₂ to 9.8 g. Hb/100 ml.*	„
4	2 weeks post partum	1,400 (100 × 14)	5.4	12.6% reticulocytosis on 6th day; Hb 8.4 g./100 ml. on 15th day, marrow then normoblastic	Changed to folic acid with continued rise of Hb to 11.9 g./100 ml. No second reticulocytosis	„
5	2 weeks post partum	1,000 (100 × 10)	3.3	26.5% reticulocytosis on 6th day, Hb 6.9 g./100 ml. on 14th day; marrow normoblastic on 7th day, with some giant metamyelocytes	Continued rise on further B ₁₂ and later iron to 15.6 g. Hb/100 ml.	„
6	At term	1,000 (100 × 10)	6.0†	31.3% reticulocytosis on 6th day; Hb 7.7 g./100 ml. on 15th day, marrow then normoblastic	Continued rise on further B ₁₂ to 11.6 g. Hb/100 ml.	„
7	„ „	100	6.5	10.1% reticulocytosis on 5th day; Hb 7.8 g./100 ml. on 15th day	Continued rise on further B ₁₂ to 13.3 g. Hb/100 ml.	Moderate
8	4 weeks ante partum	100	4.6	20.9% reticulocytosis on 8th day; no rise in Hb by 15th day, marrow then still megaloblastic	10.3% reticulocytosis on 4th day after folic acid, Hb 6 g./100 ml. 15 days later. Marrow then normoblastic. After delivery and iron Hb rose to 12.3 g./100 ml.	Reticulocyte rise only
9	4 weeks ante partum	200	6.8	No rise in reticulocytes by 5th day; Hb then 5 g./100 ml., but marrow more nearly normoblastic	22.8% reticulocytes on 7th day after folic acid, but slow rise with iron to 9.8 g. Hb/100 ml.*	Partial marrow change only
10	10 weeks ante partum	700 (100 × 7)	3.8	No rise in reticulocytes by 7th day, Hb then 3.2 g./100 ml., and marrow megaloblastic	33.1% reticulocytosis on 5th day after folic acid, Hb 5.1 g./100 ml. on 11th day. Continued rise to 8.6 g. Hb/100 ml.*	None

* Left hospital against advice. † Transfused before trial.

100 ml.), but these two groups are not strictly comparable, since the folic acid cases were usually more anaemic before treatment and could not be observed over preliminary control periods. The addition of folic acid to treatment did not seem to alter the subsequent course in two of the trial cases, while in four others who were followed long enough blood counts reached normal values on vitamin B₁₂ (with added iron in two).

Very poor results followed treatment with vitamin B₁₂ in all three cases seen during pregnancy. From Table I it is seen that total proteins and serum albumin levels were lowest in these three cases, so that, besides pregnancy, protein malnutrition might be a factor inhibiting response to treatment. This seems unlikely from my experience with folic acid series. In six cases, four treated with folic acid at term and two post partum, serum albumin was less than 3 g. per 100 ml. (range 1.6 to 2.8 g.), and in three of these the total protein was less than 6 g.; yet five responded well, including one with only 4.9 g. total protein and 2.5 g. albumin.

A similar distinction between cases treated before and after delivery is found by analysing the details of the trial reported by Moore *et al.* Ten of their 12 post-partum cases responded to the large doses they used, but in some there were only small increments in Hb in the first two weeks. Only three out of their five ante-partum cases responded to vitamin B₁₂, and in all three the average daily Hb rises were very low. On the other hand, seven of Berry's nine cases treated during pregnancy responded to vitamin B₁₂, although normal Hb levels were not reached. Like Das Gupta *et al.* (1953), who treated nutritional macrocytic anaemia with vitamin B₁₂, Berry believes that additional folic acid may be necessary for complete remission. Foy *et al.* (1955) suggest that there are two types of non-pernicious megaloblastic anaemias in Africans—classified on response to treatment—including cases seen in pregnancy. One type responds completely to penicillin (in specified doses) or to vitamin B₁₂ by mouth, and serum vitamin B₁₂ levels are very low before treatment. The other (with normal serum vitamin B₁₂ levels) responds to folic acid but not to penicillin or vitamin B₁₂.

In Durban the bone marrow differs from that described in megaloblastic anaemia seen in temperate climates. Giant metamyelocytes are always present, but erythropoiesis may be either megaloblastic or of the intermediate variety. Similar appearances are seen elsewhere in Africa. Dacie and White, who observed red-cell precursors of intermediate type in cases of pernicious anaemia not severely anaemic, ascribed the changes to minor deficiencies in haemopoietic factors. In my cases, however, as in those of Foy *et al.* (1952a) and Berry, this intermediate type of megaloblastic change may be seen when anaemia is severe.

It seems likely that there are several varieties of megaloblastic anaemia associated with pregnancy because of these differences in the appearance of the bone marrow and in response to treatment. Despite this, however, cases reported from many parts of the world have much in common. They tend to occur in the last three months of pregnancy or in the puerperium; sometimes the onset is rapid; the peripheral blood picture is inconsistent; spontaneous remission may occur after delivery; and dietary deficiencies do not appear to be the only cause, although diets are often poor. The common factor among them all may well be the development of resistance to the action of haemopoietic substances during pregnancy, as Badenoch and his colleagues have suggested, rather than to absolute deficiencies.

Summary

The results of a clinical trial using vitamin B₁₂ in 10 patients with megaloblastic anaemia of pregnancy are recorded. The appearance of the bone marrow is briefly described.

Response was satisfactory in all seven treated after delivery. It appeared to be as good with doses of 100 µg.

as it was when 1,000 µg. or more was given, but better results are usually obtained with folic acid.

Three patients treated before delivery responded poorly.

Because of differences in the appearance of the bone marrow and in response to treatment, it seems likely that there are several varieties of megaloblastic anaemia associated with pregnancy.

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REFERENCES

- Adams, E. B. (1954). *British Medical Journal*, 1, 537.
 — and Wilmot, A. J. (1953). *S. Afr. med. J.*, 27, 1028.
 Badenoch, J., Callender, S. T., Evans, J. R., Turribull, A. L., and Wits, L. J. (1955). *British Medical Journal*, 1, 1245.
 Berry, C. G. (1955). *Ibid.*, 2, 819.
 Bethell, F. H., Meyers, M. C., and Neligh, R. B. (1948). *J. Lab. clin. Med.*, 33, 1477.
 Callender, S. T. E. (1944). *Quart. J. Med.*, 13, 75.
 Chaudhuri, S. (1951). *British Medical Journal*, 2, 825.
 Clark, J. R. (1952). *Edinb. med. J.*, 59, 274.
 Cohen, I. (1953). *S. Afr. med. J.*, 27, 627.
 Dacie, J. V., and White, J. C. (1949). *J. clin. Path.*, 2, 1.
 Das Gupta, C. R., Chatterjee, J. B., and Basu, P. (1953). *British Medical Journal*, 2, 645.
 Day, L. A., Hall, B. E., and Fease, G. L. (1949). *Proc. Mayo Clin.*, 24, 149.
 Foy, H., Kondi, A., and Hargreaves, A. (1952a). *Trans. roy. Soc. trop. Med. Hyg.*, 46, 327.
 — (1952b). *British Medical Journal*, 1, 852.
 — and Manson-Bahr, P. E. C. (1955). *Lancet*, 2, 693.
 Furman, R. H., Daniels, W. B., Hefner, L. L., Jones, E., and Darby, W. J. (1950). *Amer. Practit. (Philad.)*, 1, 146.
 Ginsberg, V., Watson, J., and Lichtman, H. (1950). *J. Lab. clin. Med.*, 36, 238.
 Kothari, B. V., and Bhende, Y. M. (1949). *Indian J. med. Res.*, 37, 347.
 Moore, H. C., Lillie, E. W., and Gatenby, P. B. B. (1955). *Irish J. med. Sci.*, p. 106.
 Nieweg, H. O. (1952). *Lancet*, 2, 491.
 Patel, J. C., and Kocher, B. R. (1950). *British Medical Journal*, 1, 924.
 Tasker, P. W. G. (1954). *Lancet*, 1, 785.
 Thompson, R. B., and Ungley, C. C. (1951). *Quart. J. Med.*, 20, 187.
 Ungley, C. C., and Thompson, R. B. (1950). *British Medical Journal*, 1, 919.

OPERATIVE PARATHYROID ARTERIOGRAPHY FOR LOCATION OF PARATHYROID TUMOUR

BY

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The operative discovery of a parathyroid tumour which lies at a distance from the thyroid gland, and especially of a parathyroid tumour in the superior mediastinum, can still be a difficult surgical exercise, and any procedure which locates such a tumour is of advantage. It has been found possible, at least on some occasions, to outline a parathyroid tumour by passing an arterial catheter disto-proximally into the arch of the aorta so that its tip lies at the orifice of the subclavian artery and radio-opaque material injected by way of the catheter can enter that artery, and pass by the inferior thyroid trunk to the thyroid gland and parathyroid tumour; but filling of the vertebral artery by this technique may give cerebral complications (Seldinger, 1954). The parathyroid tumour is so vascular that it may be