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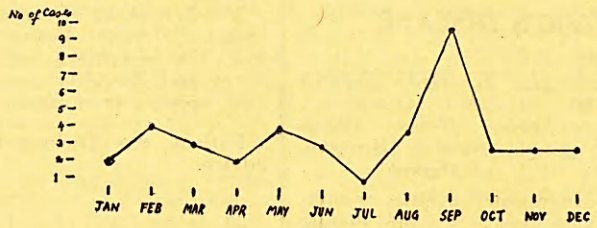

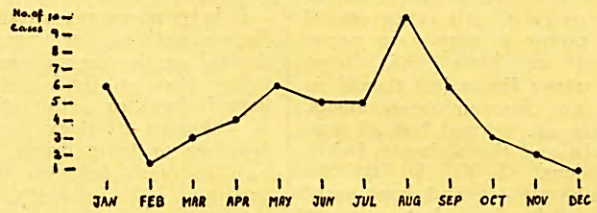

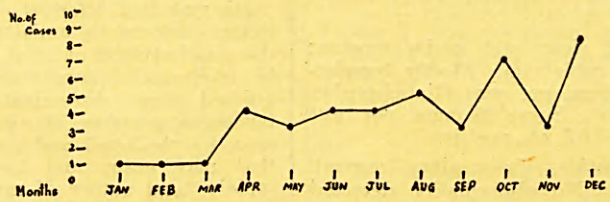

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VITAMIN B_{12} IN MACROCYTIC ANÆMIA IN PREGNANCY

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IN a recent publication (Das Gupta *et al.*, 1953) results of Vitamin B_{12} therapy in nutritional macrocytic anæmia were communicated. In the present communication the authors' experience with Vitamin B_{12} in cases of macrocytic anæmia in pregnancy is recorded.

Material and method

Uncomplicated cases of macrocytic anæmia during pregnancy, or just after confinement were selected for the study. The patients were all Indians and were treated during their stay in the Eden Hospital attached to the Medical College, Calcutta. On account of the socio-economic condition of the patients and of very great demand for maternity beds in the hospital, generally it was not possible to keep the patients in the hospital for a long time. Hence treatment with Vitamin B_{12} was started soon after completion of the basic clinical and hæmatological examinations. In the majority of the patients Vitamin B_{12} was given by intramuscular injection for 3 to 5 consecutive days in one course and in a few patients a second course was given when there was no initial improvement, when the improvement was inadequate or non-sustained *i.e.* blood values either remained stationery or declined. The degree of improvement after each course of treatment was calculated according to the formula of Della Vida and Dyke (1942) and the improvement rate was classified as given in the table.

Very good—when	the	improvement	rate	was	over	90	p.c.	of expected	improvement
Good— „	„	„	„	„	between	75 & 90	p.c.	„	„
Very fair— „	„	„	„	„		50 & 74	p.c.	„	„
Fair— „	„	„	„	„		30 & 49	p.c.	„	„
Tolerable— „	„	„	„	„		15 & 29	p.c.	„	„
Nil— „	„	„	„	„	below	15	p.c.	„	„

Dose of Vitamin B_{12}

Vitamin B_{12} was not given in any graded dose, the dose being usually determined by the amount of Vitamin B_{12} which was available. 21 cases reported in the present series fall into two broad groups:—

Group A (nos. 1 to 13) with megaloblastic bone marrow.,

Group B (nos. 14 to 21) with normoblastic bone marrow.

Group A. cases with megaloblastic marrow

(*Table I*)

(*i*) *Treated with Vitamin B_{12} given orally*: 5 patients. Five patients (nos. 8, 10, 11, 12, & 13) were treated with oral Vitamin B_{12}. With small dose (37.5 μg.) of Vitamin B_{12} one patient (no. 12) who was confined on the 2nd day of her treatment showed only fair improvement. On repeating the same dose on the 16th day, the patient showed very good improvement. No response was seen in the other four patients with dosage varing from 25 to 500 μg. Two of these patients (nos. 8 & 10) were later given Vitamin B_{12} parenterally; one of whom (no. 8) showed very good response, while the other (no. 10) showed only slight response. The remaining two patients (no. 11 & 13) who did not show any response with small dose of Vitamin B_{12} given orally, showed very good response with folic acid given subsequently.

(*ii*) *Treated with Vitamin B_{12} given parenterally*: 10 *patients*. The maximum improvement shown by any particular patient with Vitamin B_{12} is shown in Table Ia. The amount of Vitamin B_{12} given in each case is shown in parenthesis after the case numbers, while the cases where treatment was started just after confinement are marked with asterisk.

TABLE Ia

Improvement Index	No. of cases	Case nos. with dosage
Very good	6	*3, 4* & 5 (120 μg) 6 & 7 (200 μg) 8 (250 μg)
Good	1	2 (120 μg)
V. fair	2	1 (60 μg); 9 (250 μg)
Tolerable	1	10 (250 μg).

A second course of treatment with the same dose of Vitamin B_{12} was given to 2 patients (nos. 5 & 9). The response was about the same in 1 patient (no. 9) and much less in the other (no. 5). Thus no strict correlation was seen between the dose of Vitamin B_{12} and the improvement index.

Comparing the response by the two routes it was found that response by the parenteral route was definitely better than that by the oral route.

Response with other hæmatinics

(*a*) *Folic acid* was given to 5 patients. In two patients (nos. 11 & 13) it was given after oral B_{12} and in both of them the response was much better. In the remaining 3 patients (nos. 1, 2 & 5) folic acid was given after parenteral B_{12}. The first patient (no. 1) who was confined during treatment with folic acid showed slightly less response than B_{12}. The second patient (no. 2) showed about the same response but the blood picture showed difinite evidence of hypochromia during the course of treatment with folic acid and this patient later responded well to iron. The third patient (no. 5) did not improve with folic acid. This patient had previously shown very good improvement with parenteral Vitamin B_{12}, but the improvement was not sustained; still later she showed further improvement with crude liver extract given parenterally.

(*b*) *Liver extract.*—was given to only one patient, no. 5 after B_{12} and folic acid. The response was very fair and sustained. As mentioned above this patient previously showed very good improvement with Vitamin B_{12} given parenterally but did not show any improvement with folic scid.

(*c*) *Iron.*—Associated hypochromia as indicated by low M. C. H. C. was noted in as many as 6 patients, in 2 (nos. 6 & 7) before commencement of any treatment and in the remaining 4 (nos. 2, 8, 9 & 10) after B_{12} therapy. In 2 patients (nos. 2 & 8) it was possible to note the favourable effect of iron treatment while the remaining 4 patients (nos. 6, 7, 9 & 10) left hospital before any iron could be given to them.

Reticulocytosis

Adequate reticulocyte response was not seen in any of the patients either after oral or parenteral B_{12}.

Macrocytosis

Along with the rise of R. B. C. and hæmoglobin level, definite reduction in corpuscular volume was noted in the majority of the patients.

Group B cases with normoblastic marrow

TABLE II

(*i*) *Treated with Vitamin B_{12} given orally 3 patients.*—Three patients (nos. 16, 20 & 21) were given Vitamin B_{12} orally. Of these 2 (nos. 16 & 20) showed very fair and good improvement with 400 and 500 μg of B_{12} respectively while the third patient (no. 21) did not show any improvement with 500 μg. The last patient showed associated hypochromia after oral B_{12}. In patient no. 20 a second course of oral B_{21} with half the previous dose resulted in further improvement but the rate of improvement was less. About the same improvement rate was however seen in patient no. 16 when oral therapy was followed by a smaller dose of parenteral B_{12}.

(*ii*) *Treated with Vitamin B_{12} given parenterally 6 patients.*—The maximum improvement shown by any particular case with Vitamin B_{12} is shown in table IIa. The amount of Vitamin B_{12} given in each case is shown in parenthesis after case nos.

TABLE IIa

Improvement Index	No. of cases	Case nos. with dosage	
Very good	4	14 & 15	(240 μg)
		19	(500 μg)
		17	(600 μg)
V. fair	2	16 & 18	(250 μg)

Here again no strict correlation was seen between the dose of Vitamin B_{12} and the improvement index.

A second course of treatment with Vitamin B_{12} was given to 3 patients nos. 17, 18 & 19. With only half of the previous dose, same rate of improvement was maintained in patient no. 19, while with the same dose as before much better improvement was seen in patient no. 17 but no improvement was seen in patient no. 18.

As in the cases with megaloblastic marrow, response was definitely better when B_{12} was given parenterally.

Response to other haemâtinics

Folic Acid.—Was given to only one patient (no. 18) after parenteral B_{12} with much better result.

Iron.—Associated iron deficiency was suggested by the blood picture in one patient (no. 21) who left hospital soon after B_{12} therapy and before she could be given any iron.

Reticulocytosis

Except in one patient (no. 19) adequate reticulocyte response was not seen in any patient either with oral or parenteral B_{12}.

Macrocytosis

Along with increase in red cells count and hæmoglobin level, definite reduction in corpuscular volume was noted in most of the patients both after oral and parenteral B_{12}. But no definite correlation was found between the reduction in cell size and the improvement rate.

Discussion

In a previous communication it was pointed by us (Das Gupta and Chatterjea 1949) that the incidence of anaemia in the pregnant women is very high in India and that folic acid cures most of the cases of macrocytic anæmia in pregnancy. With the uniform success of Vitamin B_{12} in pernicious anaemia, it has been tried in macrocytic anaemia in pregnancy with variable results in the different parts of the world. While Day *et al* (1949), Bethell *et al* (1949), Furman *et al* (1950) and Ginsberg *et al* (1950) in the U. S. A. and Ungley & Thompson (1950) in England found Vitamin B_{12} to be ineffective, Patel and Krocher (1950) and Chaudhuri (1951) both from India, found Vitamin B_{12} to be effective in cases of anaemia in pregnancy and in puerperium. Inspite of the high incidence of such anaemia in India the number of cases reported so far during pregnancy is rather small; 4 out of 5 cases reported by Patel and Krocher and only 5 out of 16 cases reported by Chaudhuri were treated during pregnancy and the rest of the cases were treated at least 2 weeks after confinement. It is well known that with the removal of the load of pregnancy spontaneous remission or accelerated response is common during puerperium and; therefore, evaluation of the potency of a haematinic by trial during this period is hardly justified. Analysis of Indian reports show that during pregnancy 3 (nos. 1, 2 & 3) out of 4 cases of Patel and Krocher and 3 (nos. 4, 8 & 18) out of 5 cases of Chaudhuri were under observation for less then three weeks. In one patient (no. 1) reported by Patel and Krocher even during this short period the blood levels fell after good initial rise. In another of their cases (no. 4) the only patient, who was under observation for a longer period, and was given 3 successive doses of Vitamin B_{12} at an interval of 2 to 3 weeks, the blood levels fell after an initial rise on each occasion. Thus it is not possible to say whether the initial improvement observed in all these patients would have been sustained. In the present series, 16 patients (10 with megaloblastic marrow and 6 with normoblastic marrow) were treated with parenteral Vitamin B_{12} and 8 patients (5 with megaloblastic marrow and 3 with normoblastic marrow) were treated with oral Vitamin B_{12}. Three of the patients (nos. 8, 10 & 16) had parenteral Vitamin B_{12} subsequent to oral therapy. Response with parenteral Vitamin B_{12} was definitely better than the response with oral B_{12} irrespective of the nature of erythropoiesis. Erythropoiesis in group B described as normoblastic, probably needs some qualification. Our criteria for labelling an erythroblast as megaloblast are rather strict and in the present study we did not pay any particular attention to identify the transitional cells as described by Davidson *et al* (1947) Dacie and White (1947), and Israels (1951). Thus the possibility of the presence of transitional cells in some cases of this group cannot be ruled out. Recently, examination of bone marrow with a special view to find out the incidence of transitional cells in the different types of anaemia shows that these cells are not infrequently seen in cases of macrocytic anaemia with predominantly normoblastic marrow.

Initial response after parenteral therapy was good in 70 per cent of the patients with megaloblastic bone marrow and in over 80 per cent of the patients with normoblastic marrow. Thus our observations with regard to initial improvement are in agreement with results obtained by Patel and Krocher and by Chaudhuri. Incidentally it may be mentioned here that all the three patients in the present series (nos. 3, 4 & 12) in whom the treatment was started just after confinement showed very good improvement.

Though initial response had no distinct correlation with dose of Vitamin B_{12}, better response was generally found with 120 μg. or more by the parenteral route and with 300 μg. or more by the oral route. As in the case of NMA in general population, great variation in response was noted in the different patients as also in the same patient on different occasions. In the few patients who could be followed for a longer period continuation of Vitamin B_{12} failed to produce any further improvement as exemplified in 3 patients (nos. 2, 5 & 18); further improvement was seen with folic acid in 2 of them (nos. 2 & 18) but none in the third patient (no. 5) who responded well to liver extract given subsequently.

As in NMA reticulocytosis was inadequate in most of the patients. There was no correlation between the improvement rate and reticulocytosis. The reticulocytic response in the present series was definitely less than what was found by Patel and Krocher and by Chaudhuri. But unlike NMA macrocytosis was correeted to a greater extent in the majority of the patients irrespective of the route of administration and the nature of erythropoiesis. But lowering of the M. C. V. had no constant correlation with the improvement rate. Reduction in the macrocytosis is also seen in the cases reported by Patel and Krocher and by Chaudhuri.

Present studies tend to prove that Vitamin B_{12} alone would seldom restore the blood picture to normal level in macrocytic anaemia in pregnant Indian women. Tnough evidences (Das Gupta & Chatterjea, 1949; Benjamin 1948; Goodal *et al* 1948) have accumulated to show that folic acid deficiency of considerable degree is present in these cases. In view of our experience with Vitamin B_{12} and folic acid we are inclined to think that an average case of macrocytic anaemia in pregnancy represents a combined deficiency of both the factors. The present data are, however, insufficient for evaluation of the relative roles of Vitamin B_{12} and folic acid in the macrocytic anaemia in pregnancy and further work must be carried out particularly with regard to serum B_{12} level and B_{12} excretion during the different phases of treatment with B_{12}, folic acid and liver extract. Success of crude liver extract over Vitamin B_{12} and folic acid in an occasional case, as in case no. 5, is probably attributable to the Synergistic action of its constituent factors (Das Gupta *et al* 1953).

In the present series associated iron deficiency was seen in a number of patients; in 3 patients (nos. 6, 7 & 21) before institution of any treatment and in 3 others (nos. 8, 9 & 10) after parenteral B_{12}. Critical examination of blood reports show that associated iron deficiency was present in 2 of the patients (nos. 2 & 3) reported by Patel and Krocher and in two patients (nos. 9 & 15) reported by Chaudhuri before institution of any treatment and also in one patient (no. 1) of Patel and Krocher and in one patient (no. 4) of Chaudhuri after treatment with Vitamin B_{12}. This associated iron deficiency does not seem to inhibit the initial improvement rate but it is a limiting factor in securing optimum and sustained response in these cases.

Summary

Twenty one cases of macrocytic anaemia in pregnancy, 13 with megaloblastic marrow and 8 with normoblastic marrow, were treated with Vitamin B_{12} orally and|or parenterally.

In both these groups, response by the parenteral route was better than that by the oral route.

Initial response was good in about 70% of the cases with megaloblastic marrow and in 80% of the cases with normoblastic marrow. Initial response had no distinct correlation with the dose of Vitamin B_{12}, but generally better response was found with 120 μg. or more given parenterally and 300 μg. or more given orally.

Reticulocytosis after Vitamin B_{12}, oral and parenteral, was always sub-optimal. Definite reduction of corpuscular volume was noted in most of the cases, both after oral and parenteral therapy.

The good initial response noted in most of the cases was, however, not sustained and continuation of B_{12} therapy did not usually produce further improvement of blood picture but administration of folic acid and|or liver extract (crude) did.

The pathogenesis of macrocytic anaemia in pregnancy is discussed. It is suggested that an average case of macrocytic anaemia in pregnancy represents combined deficiency of folic acid and Vitamin B_{12}.

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Table I

Group A. *With megaloblastic bone-marrow:*

*0 marks the beginning and **underlined** figures the end of the period of observation.

**I.R. = Improvement rate calculated according to the formula of Della Vida and Dyke.

V.G. = Very good; G = Good; V.F. = Very Fair; Tol. = Tolerable;

Serial No.	Age	Pregnancy Grav.	Pregnancy Month	Haematini	Route	Dose Daily	Dose Total	Day* of Treat.	Hb. Gm/p. pc.	R. B. C. Mills/c.mm	M. C. V. Cu. m.	Reites p. c.	Reites Day	I. R.*.	Remarks.
1	27	3	8	Vit. B12	I. M.	20ug	60 ug	0	4.38	1.31	114.5	4.5	5		
								15	6.83	2.27	92.5			V. F.	Improvement not sustained
				Folic Acid.				**25**	4.64	.65	90.9				treatment with folic acid. Confined during course of
					Oral	30mg	510 mg	0							
								15	5.80	2.07	96.6			F.	Left.
2	17	1	8	Vit. B12	I. M.	20ug	60 ug	0	8.26	1.95	128.2	7.0	5		Placenta praevia
								15	6.09	1.75	137.7			Nil	Caesarian section.
								0							
				„	I. M.	20ug	60 ug	15	8.41	2.62	99.2			G.	
								25	8.70	2.35	119.1				Improvement not sustained.
				„	I. M.	20ug	60 ug	0							
								10	8.99	2.54	110.2			Tol.	
				Folic Acid	Oral	30mg	450 mg	0							Hypochromic blood picture.
								2	8.55	3.10	96.7			G.	
				Fe SO4	Oral	12 gr	252gr.	0							
								30	10.15	3.56	87.1				
3	28	8	9	Vit. B12	I. M.	40ug	120ug	0	4.64	1.26	135.0	2.4	4	V. G.	Treatment started on 2nd day after confinement Left
								10	7.25	2.12	108.5				
4	28	8	9	Vit. B12	I. M.	40 ug	120 ug	0	4.64	1.26	135.0	Nil			Treatment started on 2nd day after confinement Left.
								10	7.24	2.12	108.5			V. G.	
5	25	9	7	Vit. B12	I. M.	40ug	120 ug	0	3.62	1.10	109.1	16.6			
								15	7.25	2.40	108.3			V. G.	Improvement not sustained
								25	8.41	2.25	115.5				
				„	I. M.	40ug	120 ug	0							
								10	8.12	2.51	99.6			Nil	
				Folic Acid	Oral	30 mg	450 mg.	0							
								15	6.96	2.01	114.4			Nil	
				Liver extract	I. M.	3 cc.	36 cc.	0							
								10	8.41	2.32	125.0				
								25	8.70	2.87	94.0			V. F.	Improvement sustained.

6	18	1	8	Vit. B12	I. M.	40ug	200ug	0 10	5.5 7.25	1.64 2.65	140.2 113.2			V. G.	Dimorphic blood picture. Left.
7	18	1	8	Vit. B12	I. M.	40ug	200ug	0 10	5.50 7.25	1.64 2.65	140.2 113.2	5.2	7	 V. G.	Dimorphile blood picture. More hypochromic. Left.
8	28	3	8	Vit. B12 „	Oral I. M.	100ug 50ug	500ug 250ug	0 10 0 10	4.35 3.19 4.06	1.30 0.89 1.55	107.7 112.3 96.7	1.2	4	 Nil V. G.	 Dimorphic blood picture. Left hospital, readmitted & improved with Iron and Liver.
9	16	1	8	Vit. B12 „	I. M I. M.	50ug 50ug	250ug 250ug	0 10 0 10	2.90 4.64 6.38	0.96 1.44 1.93	135.4 111.1 124.3	14.8	6	 F. F.	 Dimorphic blood picture. Left.
10	19	4	7	Vit. B12 „	Oral I. M.	60ug 50ug	300ug 250mg	0 7 0 7	3.48 3.19 3.19	0.88 0.86 1.02	113.6 116.2 117.6	1.2 5.8	6 5	 Nil Slight	 Dimorphic blood picture. Left.
11	21	1	8	Vit. B12 Folic Acid	Oral Oral	5 ug 30mg	25 ug 900mg	0 7 0 15 40	4.06 4.35 7.68 9.28	1.23 1.27 2.50 3.20	105.6 110.2 104.0 96.8	 11.7	 7	 V. Slight V. G.	 Improvement rate much slower after V. G initial improvement.
12	21	3	9.	Vit. B12	Oral Oral	7. 5ug 7. 5ug	37.5ug 37.5ug	0 15 0 7	5.51 7.83 10.44	1.37 1.96 3.01	131.3 132.6 112.9			V. G.	Confined on Second day of treatment. Left.
13	39	9	9	Vit. B12 Folic Acid	Oral Oral	5 ug 30mg	60 ug 900mg	0 17 0 20 30	7.25 4.93 7.54 8.55	1.76 1.58 2.63 2.50	125.0 100.1 102.6 116.0	3.0	7	 Nil. V. F.	

Details of haematological response at days in-dicated.

TABLE II

GROUP B. *With normoblastic bone marrow*

Notations as in table I.

Serial No.	Age.	Pregnancy Grav.	Pregnancy Month	Haematinic	Route	Dose Daily	Dose Total	Day* of Treat.	Hb Gm/p.c.	R.B.C. Mills/c. mm	M. C. V. Cu.m	Retics p. c.	Retics Day	I.R.**	Remarks.
14	20	2	8	Vit. B12	I. M.	40ug	240ug	0	3.19	0.66	166.6	12.7	6		
								15	8.70	2.70	103.7			V. G.	Left.
15	18		8	Vit. B12	I. M.	40ug	240ug	0	5.51	1.32	121.2	13.9	5		
								15	8.99	2.67	101.1			V. G.	Only slight improvement over the 10 day period—Left.
16	22	2	8	Vit. B12	Oral	60ug	400ug	0	6.52	1.30	153.8	10.8	6		
						20ug		7	7.54	2.19	109.5				
								15	7.25	2.20	113.6			V. F.	
				Vit. B12	I. M.	50 ug	250ug	0							
								7	8.99	2.72	106.6				
								15	8.7	2.70	96.2			V. F.	Left.
17	18	1	6	Vit. B12	I. M.	50 ug	250ug	0	2.61	0.60	133.3	7.2	3		
								10	5.51	1.41	120.5			V. F.	
				,,	I. M.	50ug	250ug	0							
								10	8.41	2.60	123.8			V. G.	Left
18	33	12	8	Vit. B12	I. M.	50ug	250ug	0	5.51	1.64	121.9	5.9	6		
								15	7.25	2.32	103.4			V. F.	
				,,	I. M.	50ug	250ug	0							
								10	8.41					Nil.	
				Folic Acid	Oral	30mg	900mg	20	9.57	3.21	90.3			V. G.	
								37	11.02	3.38	100.0				
19	20	1	7	Vit. B12	I. M.	50ug	500ug	0	4.06	0.89	146.0	31.6	3		
								15	7.83	2.17	110.5			V. G.	
				,,	I. M.	50ug	250ug	0							
								7	8.70	2.76	90.5			V. G.	
20	25	4	7	Vit. B12	Oral	100ug	500ug.	0	5.80	1.71	111.1	16	3		
								7	7.68	2.20	108.6			G.	
				,,	Oral	50ug	250ug	0							
								15	9.28	2.78	100.7			V. F.	
21	20	2	9	Vit.B12	Oral	100ug	500ug	0	4.35	1.22	114.7	20.2	6		
								10	4.35	1.30	123.0			Nil	Dimorphicblood picture—Left