ANAEMIAS IN PREGNANCY AT NAGPUR

A Study of 75 Cases With a Note on the Influence of Anaemias on the Course of Pregnancy, Labour and Puerperium, and on the Fate of the Conceptus

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The incidence of severe anaemias of pregnancy is quite high in this part of India. It is the commonest single cause of maternal mortality in this region. 40% of the total of 117 maternal deaths in the last five years at the Daga Memorial Hospital, Nagpur, were due to severe anaemias of pregnancy.

A great deal of work has been done in the past twenty-five years on this vital problem, but an equally great deal still remains to be done. Due to the continued efforts of several workers in various parts of India, today we are much better advised as to the mode of curative treatment of this serious malady. But we are still comparatively in the dark as to the exact factors responsible for its etiology. It is because of these lacunae in our knowledge regarding the etiology of anaemias in pregnant women that we have not been able to achieve much in the way of prophylaxis of this vital disease. These considerations, coupled with the fact that no such work has yet been done in Madhya Pradesh, led to the undertaking of this present investigation.

Material: During the period from 1st October 1952 to 30th September 1953 all the clinically suspected cases of anaemia amongst all the indoor patients in the Daga Memorial Hospital were haematologically investigated. A strict watch was kept for clinical evidence of anaemia amongst the cases admitted for confinement in the maternity ward, cases admitted for any complaints in the antenatal wards as well as amongst the cases pregnant, puerperal, or non-pregnant admitted into the hospital for treatment of any other medical, surgical, or gynaecological ailment. All the cases that showed clinical evidence of anaemia were subjected to full haematological investigation. Those that were found to be more than just mildly anaemic were selected for this study. Altogether 39 pregnant, 36 puerperal, and 7 non-pregnant women were thus selected and studied.

Method. A detailed history, with regard to the socio-economic conditions, diet and previous health, was recorded in every case. Every patient was directly questioned as to the occurrence or otherwise of the following, in the recent past; loss of appetite, vomiting, diarrhoea, sore tongue, fever, dysentery, round worms, and of usual symptoms of anaemia and their duration. A detailed menstrual and obstetric history was also recorded in every case. All

the cases were subjected to a thorough clinical examination.

The following laboratory investigations were carried out in every case:

Haematological. Red cell count, haemoglobin, packed cell volume, mean corpuscular volume, mean corpuscular haemoglobin concentration and plasma proteins were determined by the methods already described in our previous paper "Blood in Pregnancy". These determinations were carried out initially and weekly after commencement of treatment. Blood smears and reticulocyte counts were made on capillary blood obtained by finger prick.

Films of bone marrow obtained by sternal puncture prior to treatment were examined in 41 cases.

Serum bilirubin was determined by a method adapted from the method of Haslewood and King, using a two celled photo-electric colorimeter.

Stool was examined microscopically for helminthic ova and protozoa. Urine was examined microscopically as well as for sugar and albumin.

Kahn Flocculation Test for syphilis was done on thirty-five patients.

Gastric analysis was done on 29 cases. Those cases who showed no free acid were tested for presence of free acid after the parenteral administration of 0.5 mg. of histamine hydrochloride.

The diet of all these patients was strictly controlled throughout the period of study. No meat, fish, eggs or liver was allowed. They were kept on usual hospital diet consisting of rice, wheat chappaties, dal and vegetables.

On the basis of haematological findings and the response to therapy, all the cases were found to belong to one of the following two main etiological types:—

(1) Erythrocyte maturation factors (E.M.F.) deficiency anaemia with or without existing iron deficiency.

(2) Pure iron deficiency anaemia.

Thus 58 cases were found to belong to the former type and 17 cases to the latter type. Out of the 58 cases of the first type, 39 were found to be of pure E.M.F. deficiency anaemia and 19 of combined E.M.F. and iron deficiency anaemia. All the seven non-pregnant patients had pure iron deficiency anaemia.

For the sake of comparison the various findings in these two main types have been analysed separately in the following pages.

The term erythrocyte maturation factors deficiency anaemia is preferred to the other names such as nutritional megaloblastic anaemia, nutritional macrocytic anaemia, pernicious anaemia and antimegaloblastic factor anaemia. It does not seem proper to call this anaemia nutritional as it is not yet fully established that this anaemia is due merely to a pure and simple nutritional deficiency. Najjar and others kept men on a synthetic diet devoid of folic acid for 18 months without clinical evidence of folic acid deprivation, presumably because the folic acid synthesis by the intestinal bacteria of these men was adequate to cope with their demands. That such synthesis does take place under normal conditions has been shown by Denko and his associates. Similarly, there is some evidence to suggest that vitamin B12 (another erythrocyte maturation factor) is

also synthesised by some bacteria in the intestinal tract (Dyke et al).

As will be seen in the following pages and as has been reported by other workers, every case of E.M.F. deficiency anaemia is not macrocytic and neither does every case of E.M.F. deficiency anaemia show megaloblasts in the peripheral blood smear or bone marrow. In view of these considerations it is felt that till such time that more is known about the exact etiology of this anaemia, the term E.M.F. deficiency anaemia is likely to be less confusing than the others and hence this term has been adhered to throughout this work (Table I).

TABLE I

Distribution of cases according to the per capita per month income of the family

Income, P.C., P.M., in Rupees ..	Between 0-15	Between 16-30	Above 30
No. of cases of E.M.F. deficiency anaemia	28	26	4
No. of cases of iron deficiency anaemia	11	4	2

Findings and Comments

Socio-economic conditions. Most of the patients belonged to the poor or the lower middle class. Table I shows that 48.3% of the cases of E.M.F. deficiency anaemia belonged to the income group of Rs. 15 per capita per month or below and 93% belonged to the income group of below Rs. 30 per capita per month or below. Similarly, 88% of the cases of iron deficiency anaemia belonged to the income group of Rs. 30 p.m. Most of the patients belonged to the working class. Their husbands were mill labourers, rickshaw pullers or weavers. A few of them belonged to the lower middle class and their husbands were either clerks or petty shop keepers. Most of them lived in the congested slums of Nagpur city. In the E.M.F. deficiency anaemia series, 52 were Hindus and 6 were Muslims, while in the iron deficiency anaemia series, 10 were Hindus and 7 were Muslims. All the 7, non-pregnant iron deficiency anaemia cases were Hindus.

Diet. Most of the patients subsisted on a diet consisting mainly of rice, wheat or juari and pulses. Their intake of milk and fruit was negligible. In the E.M.F. deficiency anaemia series, 33 were non-vegetarian and 25 were vegetarian, while in iron deficiency anaemia cases, 14 were non-vegetarian and 3 were vegetarian. In the non-pregnant iron deficiency anaemia cases 3 were non-vegetarian and 4 were vegetarian. On detailed inquiry it was found that most of the non-vegetarian patients were non-vegetarian in name only. Due to their low income they could afford to eat meat, fish or eggs only occasionally. Their consumption of vegetables which was fairly low throughout the year, became lowest during the second quarter of the year due to the relative scarcity

with consequent high prices of fresh green vegetables during this quarter. and October in this region. The relative lack of green vegetables in

TABLE II A

Percentage incidence compared to total obstetric admissions for each calendar month for 12 month period

Month	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Percentage incidence in EMF deficiency anaemia	2	1.4	—	2.2	—	6	8.1	6	6.3	4.1	3.5	7.1
Percentage incidence in iron deficiency anaemia	2	2.8	3.1	—	—	3	2.7	—	—	1.3	0.9	1

TABLE II B

Seasonal incidence

Month	Bombay Balfour 1927 in percentage	Calcutta Mitra 1937	Calcutta McSwiney 1951	Nagpur Present investigation	
				E.M.F. deficiency anaemia	Iron deficiency anaemia
January	10	4	3	2	2
February	7	2	2	1	2
March	13	1	1	—	3
April	5	5	0	2	0
May	2	3	0	—	—
June	1	6	4	6	3
July	5	8	5	9	3
August	6	6	3	10	—
September	10	11	7	11	—
October	9	12	3	6	1
November	14	10	7	4	1
December	18	18	8	7	1
TOTAL	100	86	43	58	16

Seasonal Incidence. From Table II A it can be seen that there is a definite increase in the incidence of E.M.F. deficiency anaemia from June to December. This period as already stated is preceded by a period of relative vegetable scarcity in Nagpur. The incidence of gastro-intestinal disturbances like diarrhoeas and dysenteries is the highest during the months of July, August, September the second quarter, coupled with the higher incidence of gastro-intestinal disturbances during the succeeding four months may be responsible for the increase in the incidence of this anaemia during the second half of the year. In contrast to E.M.F. deficiency anaemia, the iron deficiency anaemia shows no special preponderance in any particular quarter of the year.

From Table II B it can be seen that the seasonal incidence of anaemia in Nagpur is more akin to the seasonal incidence reported from Calcutta than the one reported from Bombay. Chatterjee reported the percentage incidence of pregnancy anaemia compared with total obstetric admissions at a Calcutta hospital. He found a marked preponderance from October to January with comparatively high percentages in September and February.

Age and Parity. Distribution of cases of E.M.F. deficiency anaemia as well as of total obstetric admissions for the corresponding period by age and by parity is shown in Tables III and IV respectively. From these tables it can be seen that no particular age or parity group shows any significant predisposition to this anaemia and hence no special etiological role can be assigned to age or parity.

Duration of Pregnancy. Distribution of cases according to duration of pregnancy at the time of admission is shown in Table V. This table shows the maximum incidence of E.M.F. deficiency anaemia after 28th week.

TABLE III

Distribution of cases by age

Age in years	15-19	20-24	25-29	30-34	Above 34	Total
No. of cases of EMF deficiency anaemia	5	22	15	10	6	58
No. of cases of iron deficiency anaemia	—	5	4	5	3	17
No. of total obstetric admissions	183	480	310	220	141	1334

TABLE IV

Distribution of cases by Parity

Parity	1	2	3	4	5	6	7	8	Above 8
No. of cases of EMF deficiency anaemia	15	10	4	6	9	3	2	4	5
No. of cases of iron deficiency anaemia	—	2	5	1	3	5	1	—	—
No. of total obstetric admissions	331	233	190	144	115	80	57	46	138
Percentage incidence in EMF deficiency anaemia	4.5	4.3	2.1	4.1	7.8	3.7	3.5	8.7	3.6

TABLE V

Distribution of cases according to duration of pregnancy

Duration of pregnancy in weeks	17-20	21-24	25-28	29-23	33-36	37-40
No. of cases of EMF deficiency anaemia	1	2	4	11	19	21
No. of cases of iron deficiency anaemia	—	—	—	—	—	17

But compared to iron deficiency anaemia, this anaemia begins to manifest itself relatively earlier in pregnancy. While all the cases of iron deficiency anaemia were seen in the last month of pregnancy, the cases of E.M.F. deficiency anaemia even of severe degree were seen as early as 18th week of pregnancy.

Associated Clinical Findings in E.M.F. Deficiency Anaemia Cases

(a) *Fever.* 52 out of 58 cases had fever due to one or more of the following causes on admission and one patient developed fever due to urinary infection after her delivery in hospital. In these febrile cases malarial infection was found in 28, urinary infection in 19, puerperal sepsis in 9, typhoid fever in 2 and tonsillitis in one case. Fever was thought to be due to dysentery alone in 3 cases. In 3 patients the low grade fever settled down with improvement in anaemia. In 3 cases, cause of fever could not be determined as they died soon after admission. Thus it can be seen that malaria, urinary infection and puerperal sepsis were the chief causes of fever in this series.

In most of the cases the fever was of a short duration, while their usual symptoms of anaemia were generally of a much longer duration. In view of this, no etiological role can be assigned to any of these fevers. Anaemia was already present before the onset of these feverish illnesses. The high incidence of these illnesses in cases of this anaemia demonstrates the predisposing influence of this anaemia on these illnesses. However, these illnesses are likely to have had an aggravating effect on the severity of anaemia and on the deterioration of the general health of the patients forcing them to seek medical relief.

(b) *Acute Bacillary Dysentery.* It, however, does appear to play a significant etiological role. Eight patients dated the onset of their symptoms of anaemia to the onset of the attack of acute bacillary dysentery. They gave history of perfectly sound health prior to the onset of dysentery. Another 8 patients gave history of aggravation of their already existing symptoms of anaemia since the onset of dysentery.

(c) *Pre-eclampsia.* 11 patients had albuminuria as well as hyperpiesia and 3 patients had only albuminuria. Thus the anaemia patients show a higher incidence of pre-eclampsia compared to the healthy pregnant women. It is difficult to say whether the pre-eclampsia is a predis-

posing factor in anaemia or whether the anaemia is a predisposing factor in pre-eclampsia. Most of the severe anaemia cases showed a definite lowering of the plasma proteins before the commencement of treatment. In all these cases, the plasma proteins rose to their normal level with the improvement in anaemia without administration of any extra proteins in their diet. This indicates that there may be a definite pathological hydraemia in this anaemia, the exact cause of which is not known. It remains to be found whether there is a disturbance of salt and water metabolism similar to the one found in pre-eclampsia in these cases of anaemia as well.

(d) *Syphilis.* Kahn test for syphilis was done on first 35 cases. It was found to be positive only in one case.

(e) *Parasitic Infestation.* Stool was examined microscopically in 36 cases, 9 patients were found to have ascariasis infection, 2 had entamoeba histolytica cysts and only one had hook worm ova.

Mode of Onset. Mode of onset was insidious in most cases. Only in 13 cases the duration of the usual symptoms of anaemia was two weeks or less while in 41 cases it was one month or more and in 19 cases it was 6 months or more. 5 patients gave history of weakness and easy fatiguability for 2 years or more which became progressively worse during their current pregnancy. Many of them did not care to seek medical advice for symptoms of anaemia like weakness, easy fatiguability, dyspnoea on exertion, giddiness, paraesthesia and oedema, but sought medical advice because of the onset of labour or some other illness. The chief reason for seeking medical advice was onset of labour in 13 cases, fever in 19 cases, dysentery in 5 cases, and diarrhoea in 5 cases. Only 16 cases sought medical relief for symptoms of anaemia per se, i.e. 9 for marked oedema of lower extremities or general anasarca, 3 for dyspnoea or exertion and weakness, 3 for weakness and stomatitis and 1 for giddiness.

TABLE VI

Symptoms & Signs

Symptoms	No. of cases	Signs	No. of cases
Weakness and easy fatiguability	50	Pallor of mucous membranes & nails	58
Numbness and tingling in the extremities	25	Oedema of lower extremity only	22
Fever	52	Oedema of whole body	26
Anorexia	31	Enlarged heart and haemic murmur	45
Glossitis and or stomatitis	31	Koilonychia	15
Vomiting	10	Enlarged spleen	2
Diarrhoea	19	Glossitis and stomatitis	14
		Jaundice	6

Symptoms and Signs of E.M.F. Deficiency Anaemia

The various symptoms complained of and the various signs detected along with their frequency of occurrence are shown in Table VI. From this table it can be seen that most of the patients complained of weakness and easy fatiguability. Some of them complained of palpitations, faintness, vertigo, dyspnoea on exertion, and numbness and tingling in the extremities. All these are the usual symptoms of any anaemia. There were no symptoms specific to this anaemia.

The high incidence of fever has already been referred to and commented upon.

The common occurrence of gastro-intestinal symptoms, i.e. glossitis, stomatitis, diarrhoea, vomiting and anorexia is also very striking. These symptoms were complained of 91 times by 58 patients. Only 7 patients gave no history of any of these symptoms or dysentery throughout their pregnancy. 6 of these 7 cases gave history of fairly acute onset of symptoms of anaemia. Although they were severely anaemic on admission, the duration of their symptoms of anaemia was less than two weeks.

The remaining 51 patients complained of either one or more of these symptoms and or of acute bacillary dysentery during some part or the other of their current pregnancies. In a number of cases these symptoms were present at the time of admission to the hospital. The influence of bacillary dysentery on this anaemia has already been referred to.

In 29 cases the onset of these gastro-intestinal symptoms was coincident with or subsequent to the onset of the other symptoms of anaemia. While in the remaining 29 cases, the other symptoms of anaemia were preceded by the gastro-intestinal symptoms for varying intervals.

Whether these symptoms are primarily responsible for anaemia or not is difficult to say. May be, that these symptoms themselves are the result of the deficiency of folic acid or co-existing deficiencies of other factors of vitamin B complex, and hence are really the manifestations of a composite deficiency rather than its cause. The work of Odland et el appears to suggest that folic acid helps to further the utilization of riboflavin. Spies, as a result of his findings, considers that folic acid added to an adequate diet enhances the intestinal production and absorption of niacin. Be this as it may, these symptoms in turn are bound to aggravate the existing deficiencies and worsen the anaemia. Many of the patients who had been subjected to attacks of glossitis and or stomatitis volunteered the information that because of the sore mouth and or the sore tongue, they had been living on sweet semi-solid foods like sago and suji, devoid of green vegetables and other articles of diet containing folic acid and other factors of vitamin B complex for considerably long periods.

As a result of follow up of treatment of these cases it was found that in most cases diarrhoea and anorexia were controlled by the folic acid or the crude liver extract administered for the treatment of anaemia. In some cases the diarrhoea failed to yield to folic acid and crude liver ex-

tract but yielded to amoebicides and was thought to be due to chronic amoebiasis.

The glossitis and stomatitis was also fully relieved by folic acid. In one case the glossitis and stomatitis failed to respond to vitamin B complex given parenterally but responded to folic acid.

Signs. As can be seen from the Table VI none of the signs were specific of this anaemia. There was a far greater tendency to marked oedema of lower extremities or whole body in cases of severe anaemia due to E.M.F. deficiency as compared to the cases of severe anaemia due to iron deficiency. This finding is again suggestive of some disturbance of salt and water metabolism in cases of E.M.F. deficiency anaemia. Out of 3 cases of severe anaemia due to iron deficiency 2 that had pitting oedema upto the knees also had hypertension and albuminuria and so their oedema was probably due more to toxaemia than to anaemia. The third patient who had no co-existing toxaemia had no oedema at all, while in the E.M.F. deficiency anaemia series only 3 out of the 43 severe cases had no oedema.

Haematological Findings. The various haematological findings of 28 patients of E.M.F. deficiency anaemia, before and after treatment, are shown in Tables X and XI, and those of the remaining patients of this anaemia have already been published in our previous paper.

The distribution of all the cases of E.M.F. deficiency anaemia and of iron deficiency anaemia according to their morphological type are shown in Table VII. For the sake of comparison the E.M.F. deficiency anaemia cases have been divided into two groups, those without co-existing iron deficiency (group I) and those with co-existing iron deficiency (group II). In all but one case the co-existing iron deficiency became manifest only during the course of treatment. This deficiency manifested itself by a fall in M.C.H.C. or by levelling off of the response. On administration of iron the response improved a great deal and M.C.H.C. rose to normal level.

For the morphological classification, Wintrobe's figures for the normal range of m.c.v. and m.c.h.c. were adopted, i.e. m.c.v. of above 94 c was considered indicative of macrocytosis

TABLE VII

Morphological Classification of these cases

		Macrocytic	Normocytic	Microcytic
E.M.F. deficiency anaemia, Group I	Orthochromic	29	10	—
	Hypochromic	—	—	—
E. M. F. deficiency anaemia, Group II	Orthochromic	11	6	1
	Hypochromic	—	1	—
Iron deficiency anaemia	Orthochromic	1	4	4
	Hypochromic	—	1	7

and m.c.v. of below 80 c was considered indicative of microcytosis. M.C.H.C. of below 30% was considered indicative of hypochromia. The incidence of macrocytosis is greater in group I as compared to group II. The average m.c.v. of group I was 112 c and was much greater as compared to the average m.c.v. of 98 c of group II. This finding demonstrates the m.c.v. reducing influence of co-existing iron deficiency. In group I, 7 patients died early in the course of their treatment and 3 left the hospital early in the course of their treatment. So the co-existing iron deficiency which might have manifested itself during the course of treatment could not be excluded in these cases. Hence they were excluded while calculating the average m.c.v. of this group. Similarly, one patient of Group II that died 2 days after commencement of treatment was also excluded while calculating the average m.c.v. of this group. In the whole series of E.M.F. deficiency anaemia there was only one patient of microcytic type (case No. 23, Table XI). Her M.C.H.C. was within normal range. The only immature erythrocytes seen in her blood smear were the normoblasts. As she was extremely ill, sternal puncture was not done on her. She died 2 days after commencement of therapy so the exact diagnosis in her case remained unconfirmed. It was presumed that she was a case of combined E.M.F. and iron deficiency. None of our pure E.M.F. deficiency anaemia cases were of microcytic type. In the iron deficiency anaemia series the one case that is classed as macrocytic had the m.c.v. of 100 c only.

The distribution of cases according to their severity is shown in Table VIII. Those with haemoglobin below 6 grammes per 100 c.c. and packed cell volume below 17% were classed as severe. Those with haemoglobin value of 6 grammes to 8.5 grammes per 100 c.c. and packed cell volume of 17% to 25% were classed as moderate and those with haemoglobin value of 8.6 to 9.9 grammes

TABLE VIII

Distribution of cases according to etiological type and severity.

	Severe	Moderate	Mild
E.M.F. Deficiency Anaemia Group I			
No. of cases	29	10	—
E.M.F. Deficiency Anaemia Group II			
No. of cases	15	4	—
Iron Deficiency Anaemia			
No. of cases	3	10	4

per 100 c.c. and packed cell volume of between 25% and 29% were classed as mild.

From Table VIII it can be seen that the majority of the cases of E.M.F. deficiency anaemia (groups I and II) were of severe degree, while the majority of iron deficiency anaemia cases were of moderate degree. In E.M.F. deficiency anaemia series, haemoglobin value was between 2 to 4 grammes per 100 c.c. in 18 patients, between 4 to 6 grammes per 100 c.c. in 26 patients, between 6 to 8 grammes per 100 c.c. in 14 patients. Similarly, the red cell count was below one million in 18 patients, between 1 and 2 millions in 32 patients, between 2 and 3 millions in 8 patients.

Marrow. The marrow was examined in 41 cases of E.M.F. deficiency anaemia. Megaloblasts were found in the marrow of 25 cases only. The other 16 cases showed normoblastic hyperplasia.

Biochemical Findings

Plasma Proteins. Plasma proteins were determined on admission in 43 patients of E.M.F. deficiency anaemia cases. 38 of these patients were found to have hypo-proteinaemia, i.e. total protein value of below 6 grammes per 100 c.c. Out of these, 14 had a total protein value of between 4 and 5 grammes per 100 c.c. and 24 had a total protein value of between 5 to 6 grammes per 100 c.c. In all these cases plasma protein levels rose to normal levels with the improvement in anaemia without the administration of any extra protein foods or supplements. This fact lends support to the belief that there is an actual excessive dilution of blood in cases of anaemia. Plasma proteins were also done on 12 cases of iron deficiency anaemia. In 5 patients, the plasma proteins were between 5 to 6 grammes and in one patient between 4 to 5 grammes per 100 c.c. and in the rest above 6 grammes per 100 c.c. In these cases also the plasma proteins rose to their normal value without any additional protein foods during the course of treatment. But the incidence as well as the severity of hypoproteinaemia was much greater in E.M.F. deficiency anaemia cases compared to iron deficiency anaemia cases and hence presumably the incidence and degree of haemodilution is probably also greater in the former type. This finding coupled with the finding of higher incidence and extent of oedema in E.M.F. deficiency anaemia cases makes one suspect the existence of some coincident disturbance of salt and water metabolism in the cases of this anaemia.

Serum Bilirubin. Serum bilirubin was estimated on 39 patients of E.M.F. deficiency anaemia. It was below 1 mg. per 100 c.c. in 23 cases, between 1 and 2 mg. in 13 cases and above 2 mg. in only 3 cases. All 3 patients with serum bilirubin between 2 to 3 mg. were jaundiced; one of them had malignant tertian malaria and one had syphilis. Amongst the cases with serum bilirubin between 1 and 2 mg., 7 had malaria and 2 were jaundiced and only one of these jaundiced patients had malaria.

Gastric Analysis. Gastric analysis was done on 29 cases of E.M.F. deficiency anaemia. 10 to 65 c.c. of N/10 HCl per cent were taken as normal

limits of free acidity as recommended by Napier and Neal Edwards. On this basis 23 patients had normal acidity, 2 had hypochlorhydria, 1 had hyperchlorhydria, and only 3 had histamine-fast achlorhydria.

Thus the incidence of histamine fast achlorhydria amongst the cases examined in this series was about 10%. This is somewhat higher than the incidence of 4 to 8 per cent in the general population in India reported by several workers.

Diagnosis. The diagnosis of E.M.F. deficiency anaemia is not a simple matter. No specific signs or symptoms of this anaemia were encountered in any of the cases in this series. This anaemia, however, was found to be generally of a severer degree compared to iron deficiency anaemia. It was also found to be much commoner than the iron deficiency anaemia. The incidence of marked oedema was a more conspicuous feature of this anaemia as compared to the iron deficiency anaemia. It showed no special predisposition for any particular age or parity group. But it showed a definite seasonal variation, being much commoner in the second half of the year. It was generally seen much earlier in pregnancy than the iron deficiency anaemia. Hence a clinically typical case of E.M.F. deficiency anaemia in pregnancy may be described as a woman about 28 weeks' pregnant with very marked pallor of her skin and mucus membranes, having general anasarca with a bloated apathetic face and a pale waxy skin, seeking admission to hospital in the second half of the year. The clinical diagnosis of the cases conforming to the above typical description was invariably proved correct by the haematological findings and the therapeutic response. It must, however, be mentioned here that though most of the cases conformed to this description, quite a number did not.

Similarly great variation was found in the erythrocyte morphology in this anaemia. Although 69% of the cases were of macrocytic orthochromic type, no particular morphological type could be considered absolutely pathognomic of this anaemia (Table VII). In the same way, absence of megaloblasts in the peripheral blood smear or in the marrow smear could not be depended upon entirely to exclude its diagnosis.

Full haematological examination coupled with response to therapy was found absolutely necessary to arrive at correct diagnosis in every case. Macrocytosis, presence of immature erythrocytes in peripheral blood smear, presence of megaloblasts in the marrow and response to therapy were the chief criteria adopted for diagnosis in this series. Patients, with macrocytic orthochromic or normocytic orthochromic anaemia, with the presence of immature red cells (erythroblasts or megaloblasts) in the peripheral blood smear, and/or with the presence of megaloblasts in the marrow, were provisionally diagnosed as of E.M.F. deficiency anaemia. 52 patients were provisionally diagnosed as of E.M.F. deficiency anaemia on these criteria. In all these cases, except the 6 who expired within a few days of commencement of therapy, the diagnosis was proved correct by their subse-

quent response to folic acid or crude liver extract. While patients with microcytic hypochromic, normocytic hypochromic and normocytic orthochromic anaemia with no immature erythrocytes except an occasional normoblast in their peripheral blood smear, were provisionally diagnosed as of iron deficiency anaemia and were put on treatment with oral or intravenous iron. The error of diagnosis was much greater in this group, especially in the normocytic orthochromic cases, with anaemia of moderate degree. 6 out of 23 cases initially diagnosed as of iron deficiency anaemia failed to respond to iron. 4 of these had anaemia of moderate degree and 2 of severe degree. Anaemia was of normocytic orthochromic type in 5 cases and of normocytic hypochromic type in one.

Occasional normoblasts were the only immature erythrocytes found in the initial peripheral blood smear of these cases. In 4 of them the erythroblasts or megaloblasts appeared in the subsequent blood smears with further deterioration of anaemia and increase in m.c.v. All 6 cases were subsequently put on treatment with crude liver extract or folic acid; 2 died early in the course of treatment and one left the hospital soon after commencement of the treatment. The other 3 showed good response and thus proved the initial diagnosis to be incorrect. In contrast 5 cases with normal M.C.H.C. and normal or slightly raised m.c.v. (iron deficiency anaemia cases, Table VII) showed good response to oral iron alone. Similarly, 4 cases of iron deficiency anaemia which responsed well to oral iron alone also showed occasional normoblasts in their peripheral blood smear. This shows that the anaemia in cases with normal or slightly raised m.c.v. and normal M.C.H.C. with occasional normoblasts in their peripheral blood smear can be due to iron deficiency or to E.M.F. deficiency. As has been reported in our previous paper, the E.M.F. deficiency anaemia in its early stages is of normocytic orthochromic type, that it is only with further deterioration of haematological standards that macrocytosis appears. It is in such doubtful cases that the therapeutic response is of invaluable assistance in the differential diagnosis.

The Effect of Anaemia on Pregnancy, Labour and Puerperium.

Pregnant patients with E.M.F. deficiency anaemia are poor obstetrical risks. They stand the strain of labour badly. They tend to deliver prematurely. The tendency to *premature delivery* is more marked in cases of severe anaemia. In this series the premature delivery rate (premature labour and miscarriages) was 44.2% for the severe anaemia cases and 28.6% for the moderate anaemia cases of E.M.F. deficiency anaemia. While the premature delivery rate for the iron deficiency anaemia cases was only 6%.

The delivery was spontaneous in all the cases. In none of the cases was the labour unduly prolonged. The average duration of labour for 42 cases (of E.M.F. deficiency anaemia) that delivered in hospital was 8 hours. The average blood loss at delivery for these cases was 4.4 ounces. The blood loss was 10 ounces or

more in only 4 cases, i.e. 10 ounces in 2 and 12 ounces in the other 2.

In 37 cases, the presentation was vertex and in 5 cases it was breech. There were no other obstetrical complications in any of these cases.

In view of these findings the main cause for the increased maternal mortality following labour in these cases appears to be the *sudden increase in the blood volume* which has been shown to occur normally during labour by Tatum. This author in his study of 45 patients found that the increase in plasma volume began to manifest itself late in labour and reached its peak at approximately the same time as the placenta was delivered. They found the average rise of 3.9 c.c. per pound body weight. This is quite a significant rise and coming on suddenly as it does, it is likely to add to the load of already decompensated heart and precipitate fatal *cardiac failure*. Tatum's findings should caution us against the use of blood transfusion in these cases during or immediately after labour which is really the most critical period.

TABLE IX

Complications of Pregnancy and Puerperium with E.M.F. Deficiency anaemia

Complication	No. of cases
Urinary tract infections ..	19
Malaria	24
Puerperal Sepsis ..	9
Pre-eclampsis	11
Albuminuria	3
Typhoid	2
Acute bacillary dysentery ..	16
Ascariasis	9
Ankylostomiasis ..	1
Entamoeba histolytica cysts	2
Syphilis	1

Apart from this increased risk to life following labour, these patients are very *susceptible to various infections* during pregnancy and puerperium as can be seen from Table IX. These infections coupled with the increased liability of these patients to pre-eclampsia are responsible for the further increase in mortality and morbidity of these cases during pregnancy and puerperium. In this series 2 cases died of typhoid and one of severe malaria during their puerperium and one died of dysentery during her pregnancy. 4 patients died of cardiac failure, 3 within 24 hours of delivery and one 4 days after delivery. Thus there was a gross maternal mortality rate of approximately 14% in this series. 7 of these patients who died were severely anaemic and one was moderately anaemic. The latter died of haemorrhage from typhoid ulcers. So in this case the chief cause of death was typhoid. On excluding this case the corrected mortality is about 12%. 86% of the deaths were after delivery and only 14% before delivery. This is a significant finding. It stresses the need for delaying the onset of labour as long as possible and cautions us against attempting early termination of pregnancy by artificial means. The maternal mortality for the iron deficiency anaemia cases was nil. From the foregoing, it appears that the prognosis for the mother is worst when anaemia is due to the deficiency of E.M.F. and is of severe degree.

Fate of Conceptus

In E.M.F. deficiency anaemia series, 4 patients left the hospital before delivery. One died undeliver-

ed. 2 patients had miscarriages, one at the 18th week and the other at the 24th week of her pregnancy. 21 patients delivered prematurely; 13 of these premature infants were either still-born or died within a few days of their birth. The remaining 30 patients delivered at term, and of these, 6 were either still-born or died soon after birth. So foetal loss is considerably heavy in this anaemia in pregnancy there being a gross foetal loss of 39.6%. The foetal loss was heaviest for the severe anaemic cases, i.e. 41.0% while for the moderately anaemic cases it was 35.7%. So there appears to be a definite correlation between the severity of anaemia and the foetal prognosis. The severer the anaemia the greater the foetal loss. When the severe anaemia was due to iron deficiency alone, the foetal loss was nil. In the whole iron deficiency anaemia series there was only one premature stillbirth due to cord prolapse with compound presentation. All the others delivered at term and their infants were alive and well till the time of discharge from the hospital. This indicates that E.M.F. deficiency is far more damaging to the conceptus than pure iron deficiency. This fact also lends support to the assumption that folic acid is vitally concerned with the foetal growth and development.

Treatment

Hospitalisation with absolute bed rest is considered absolutely essential for all severe anaemia cases. However, in the study, all the cases were hospitalised regardless of the severity of their anaemia in order to keep a better control on the administration of haematinics and to ascertain their haemopoitic activity at regular intervals. No attempt at artificial termination of pregnancy was made in any of these cases, as it was found that spontaneous termination of pregnancy did not relieve anaemia. But on the contrary, the strain of labour was found to add to the load of the already overstrained heart and increase the risk of fatal cardiac failure. Puerperium also tended to be quite stormy in the severe anaemia cases. So it was considered best to leave the pregnancy quite undisturbed in these cases. Those cases that commenced labour spontaneously while still severely anaemic were kept well sedated throughout labour to lessen the cardiac strain. Those that showed evidence of cardiac distress, i.e. unduly increased pulse and respiration rate were administered digitalis and oxygen.

Blood transfusions were not given to any of these patients.

Haematinics

15 patients were treated with folic acid, 2 patients were treated with folic acid and vitamin C, 12 patients were treated with folic acid and vitamin B_{12}. The results of therapy in these 29 cases have been published already. One patient left the hospital soon after commencement of therapy with folic acid and vitamin B_{12}.

The remaining 28 cases were treated with proteolysed whole liver extract (cipalon) which is guaranteed to have a constant minimum of over

10 mcg. vitamin B_{12} activity per c.c. by the manufacturers. Only 6 puerperal patients were given 2 c.c. of this liver extract intramuscularly on alternate days but all the other patients were given 2 c.c. daily throughout the course of treatment. The results of treatment of these cases are shown in Tables X and XI.

All the cases of iron deficiency anaemia were treated with oral iron only and they all responded well to it.

Results

The results of treatment with crude liver extract of pregnant patients are shown in Table X and the results of treatment of puerperal patients as well as of those pregnant patients who delivered within a few days of commencement of therapy are shown in Table XI.

From Table X it can be seen that, out of the 5 pregnant patients treated with crude liver extract, only one showed good response during pregnancy. 2 patients showed practically no response during pregnancy and only fair response after delivery. The average rate of improvement was also much slower than with folic acid.

From Table XI it can be seen that only 4 puerperal patients showed over 100%, and 2 patients nearly 100%, of the expected weekly increase in red cells for the first two weeks. In 4 patients there was further deterioration of anaemia. Two of these died and the other two showed better response after the first two weeks when the co-existing malaria and acute bacillary dysentery had been controlled. Three other patients died within one week of commencement of therapy. One went home a week after commencement of therapy. One went home only 6 days after commencement of therapy. The remaining 8 patients showed fair initial response. The average rate of final improvement was also slower as compared to the rate of final improvement on folic acid. No difference in response was noted between patients receiving crude liver extract intramuscularly daily and those receiving the same dose on alternate days. Two cases out of the 29 cases reported previously also failed to show any response to crude liver extract, 2 c.c. of which were given on alternate days for 10 days. On the contrary their anaemia became worse in spite of liver extract. Thus altogether 6 puerperal and 2 pregnant patients failed to show any response in the first two weeks of therapy with crude liver extract.

From the comparison of results obtained in this series, it appears that folic acid is a far more potent haematinic in the E.M.F. deficiency anaemia cases in pregnancy and puerperium than the crude liver extract. Besides the ease of administration of folic acid by oral route is also a definite advantage over the parenteral administration of crude liver extract. The chief disadvantage of folic acid at present is its prohibitive cost. Although its price has been recently reduced to almost half of its previous cost, it still is beyond the means of the poor people who need it the most.

TABLE X

Results of treatment with crude liver extract in pregnant patients.

Duration of pregnancy in weeks	Haemogram before treatment				Haemogram after treatment				Treatment			Rate of increase of R.b.c. per week for 1st 2 weeks		Remarks
	H.B. in G	R.b.c. in millions	M.C.V. in Cu.	MCHC per cent	H.B. in G	R.b.c. in millions	M.C.V. in Cu.	MCHC per cent	Haematinic	Dose	Days	Actual	Expected	
28	5.5	1.3	115	36.6	7.4	2.75	91	29.6	Crude liver extract	2 cc daily	35-15AP 20 PP	.05	0.65	No response during pregnancy. Had urinary infection and diarrhoea fair response after delivery —very good response on iron & liver extract.
					11.1	4.26	82	31.7	,, & Ferrous Sulphate	9 gr.	15			
22	4.3	1.3	100	33.3	10.6	3.4	94	33.2	Crude liver extract	2 cc daily	35	0.27	0.65	Initial response slow had M.T. malaria. Final improvement good.
34	6.2	1.8	100	34.4	11.7	4.6	80	32.0	Crude liver extract	2 cc daily	36 47 AP 11 PP	0.54	0.52	Very good response in spite of urinary infection and positive K.T.
34	2.5	0.63	87	45.4	expired 2 days after commencement of crude liver extract.									Had acute bacillary dysentery.
36	5.7	1.5	107	34.9	6.4	2.35	89	30.5	Crude liver extract	2 cc daily	22 36-12	0.035	0.60	Very poor response during pregnancy. Had acute bacillary dysentery for 1st week and good response after delivery with simultaneous administration of liver extract and iron.
					10.2	3.75	86	31.3	,, & Ferri et ammonium citrate	90 gr.	14			

TABLE XI

Results of treatment with crude liver extract in puerperal patients.

Serial Number	Days since or before delivery	Haemogram before treatment				Haemogram after treatment				Treatment			Reticulocyte Peak		Rate of increase of Rbc per week for 1st 2 weeks		Remarks
		HB in G	Rbc in millions	mcv in Cu.	MCHC %	HB in G	Rbc in millions	mcv in Cu.	MCHC %	Haematinic	Dose	Days	Actual	Expected	Actual	Expected	
1.	4 PP	3.0	0.67	134	33.3	12.0	4.0	87	34.6	Crude liver extract	2 cc. alt. days	33	14	57.8	1.13	0.78	Very good response in spite of M.T. malaria.
2.	9 PP	4.0	0.96	125	33.3	11.4	4.0	89	36.1	Crude liver extract	2 cc. alt. days	33	14.4	41.13	0.82	0.72	Very good response in spite of puerperal sepsis.
3.	2 PP	5.4	1.05	143	36.0	12.4	3.23	111	36.1	Crude liver extract	2 cc. alt. days	32	14.3	38.62	0.4	0.7	Response fair. Had severe and resistent urinary infection.
4.	1 PP	5.0	1.93	82	31.2	6.2	1.83	108	31.0	Ferri et ammonium citrate	90 gr.	13	11	21.5	0.43	0.53	Response fair. Had acute bacillary dysentery followed by severe malaria. m.c.v. increased and megaloblast appeared in blood smear while on iron.
						10.7	4.0	85	31.7	Crude liver extract	2 cc. alt. days	46					
5.	2 AP	4.6	1.6	84	33.8	4.4	1.1	107	37	I. v. Iron	580 mg.	in 7days	3		—0.5		Response very poor. Had severe malaria. Expired.
						4.2	0.9	105	44	Crude liver extract	2 cc. alt. days	8	7	37.29	—0.2	0.69	
6.	50 PP	4.3	1.12	114	33.0	11.2	3.3	97	35.0	Crude liver extract	2 cc. alt. days	38	15	36.76	0.35 0.54 for the subsequent 2 weeks	0.69	Initial response fair. Had severe urinary infection. Final improvement good.

TABLE XI—(Continued)

TABLE X

Results of treatment with crude liver extract in pregnant patients.

Duration of pregnancy in weeks	Haemogram before treatment				Haemogram after treatment				Treatment			Rate of increase of R.b.c. per week for 1st 2 weeks		Remarks
	H.B. in G	R.b.c. in millions	M.C.V. in Cu.	MCHC per cent	H.B. in G	R.b.c. in millions	M.C.V. in Cu.	MCHC per cent	Haematinic	Dose	Days	Actual	Expected	
28	5.5	1.3	115	36.6	7.4	2.75	91	29.6	Crude liver extract	2 cc daily	35-15AP 20 PP	.05	0.65	No response during pregnancy. Had urinary infection and diarrhoea fair response after delivery —very good response on iron & liver extract.
					11.1	4.26	82	31.7	,, & Ferrous Sulphate	9 gr.	15			
22	4.3	1.3	100	33.3	10.6	3.4	94	33.2	Crude liver extract	2 cc daily	35	0.27	0.65	Initial response slow had M.T. malaria. Final improvement good.
34	6.2	1.8	100	34.4	11.7	4.6	80	32.0	Crude liver extract	2 cc daily	36 47 AP 11 PP	0.54	0.52	Very good response in spite of urinary infection and positive K.T.
34	2.5	0.63	87	45.4	expired 2 days after commencement of crude liver extract.							Had acute bacillary dysentery.		
36	5.7	1.5	107	34.9	6.4	2.35	89	30.5	Crude liver extract	2 cc daily	22 36-12	0.035	0.60	Very poor response during pregnancy. Had acute bacillary dysentery for 1st week and good response after delivery with simultaneous administration of liver extract and iron.
					10.2	3.75	86	31.3	,, & Ferri et ammonium citrate	90 gr.	14			

Days since or before delivery	Haemogram before treatment				Haemogram after treatment				Treatment		Reticulocyte Peak		Rate of increase of Rbc per week for 1st 2 weeks		Remarks
	HB in G	Rbc in millions	mcv in Cu.	MCHC %	HB in G	Rbc in millions	mcv in Cu.	MCHC %	Haematinic	Dose	Days	Actual	Expected	Actual	Expected	
1 PP	7.2	2.07	101	34.3	10.4	4.0	83	31.3	Crude liver extract	2 cc. daily	48	—	—	—0.27	0.51	Initial response very poor. Had severe B.T. malaria and acute bacillary dysentery. Good response in 3rd-5th week which slowed down in 6th week. Further good response to oral iron alone in 7th week.
					12.0	4.47	81	33.1	Ferri et ammonium citrate	90 gr.	7					
1 PP	4.7	1.44	100	31.7	10.8	4.3	83	30.0	Crude liver extract	2 cc. daily	37	—	—	0.77	0.64	Very good response in spite of B.T. malaria.
1 PP	4.8	1.4	94	36.3	7.7	2.9	83	32.0	Crude liver extract	2 cc. daily	26	—	—	0.24	0.65	Initial response poor. Had acute bacillary dysentery and malaria. Good response in 2nd and 3rd weeks which levelled off in 4th week. But improved again on simultaneous administration of iron.
					12.0	4.3	85	32.8	& Ferri et ammonium citrate	90 gr.	26					
4 AP	5.5	2.0	80	34.2	8.7	3.8	76	30.0	Crude liver extract	2 cc. daily	49	—	—	—0.46	0.52	Initial response poor. Lost 9 ozs. of blood at delivery on 5th day of therapy. Had dysentery and malaria. Final improvement fair.
					10.5	3.95	83	31.8	& ferrous sulphate	12 gr.	10					
1 PP	7.0	2.37	80	36.8	7.7	3.0	70	36.6	Cr. L. ext.	2 cc. daily	26					Good initial response during the 1st two weeks which levelled off. Further response to folic acid and iron.
					8.3	3.98	65	31.5	Folic acid	15 mg.						
					9.2	4.0	74	31.1	Ferrous sulphate	12 gr.	15 7	—	—	0.40	0.43	

2 AP	4.5	1.4	93	34.5	2.4	0.54	130	34.2	Crude L. extract.	2 cc. daily	9	—	—	Fell by 0.86 in 1st week		Became worse in spite of treatment. Had typhoid and expired.
13PP	2.6	0.74	108	32.5	6.2	2.46	86	29.2	Crude L. extract.	2 cc. daily	21	—	—	0.54	0.77	Fair initial response. Had acute bacillary dysentery and puerperal sepsis. Final improvement good. Iron also given due to fall in M.C.H.C.
					10.2	3.9	88	29.9	„ & ferrous sulphate	9 gr.	14	—	—	—	—	
					11.7	4.6	84	30.0	„ alone	9 gr.	7	—	—	—	—	
5 AP	3.7	1.2	80	38.9												Expired one hour after delivery on 5th day of treatment.
2 AP	8.0	2.38	92	36.1	11.2	3.9	89	32.0	Crude L. extract.	2 cc. daily	21	—	—	0.66	0.44	Very good response in spite of acute bacillary dysentery.
1 AP	4.7	1.36	81	42.7	—	—	—	—	Crude L. extract.	2 cc. daily	Went home against medical advice on 6th day of therapy					
4 PP	3.7	1.36	84	32.2	4.7	1.86	87	29.0	Crude L. extract. alone.	2 cc. daily	7		—	0.61	0.66	Good response in spite of malaria.
					10.4	4.2	81	30.6	„ and ferrous sulphate	12 gr.	21	—	—			
2 PP	4.0	1.05	95	40.0	4.7	1.3	115	31.3	Crude L. extract. alone.	2 cc. daily	7					Good response in spite of malaria.
					12.3	4.1	91	32.8	„ and ferrous sulphate	12 gr.	21	—	—	0.65	0.70	
9 AP	2.7	0.68	117	33.7	2.77	0.73	120	31.4	Crude L. extract alone.	2 cc. daily	7	—	—	—	—	Initial response very poor. Had urinary infection.
					11.4	3.9	85	34.1	„ and ferrous sulphate	12 gr.	40	—	—	.06	.78	Good response after delivery.
					11.7	4.4	84	31.6	„ alone		7	—	—	—	—	

Number	Days since or before delivery	Haemogram before treatment				Haemogram after treatment				Treatment			Reticulocyte Peak		Rate of increase of Rbc per week for 1st 2 weeks		Remarks
		HB in G	Rbc in millions	mcv in Cu.	MCHC %	HB in G	Rbc in millions	mcv in Cu	MCHC %	Haematinic	Dose	Days	Actual	Expected	Actual	Expected	
	30PP	7.7	2.6	80	38.5	8.4	3.38	80	31.1	Crude L. extract alone.	2 cc. daily	14	9.5	—	0.39	0.38	Very good response in spite of pelvic inflammation.
						11.7	3.9	94	32.0	,, and ferrous sulphate	12 gr.	14					
	43PP	4.9	1.55	95	33.1	4.9	1.8	83	32.6	Crude L. extract.	2 cc. daily	7	Went home against advice.				
	1 PP	6.5	2.45	81	32.5	5.7	1.83	94	33.1	Ferri et ammonium citrate	90 gr. 200 mg.	7					
						5.8	1.7	100	34	T.V. iron	daily	7	Had typhoid. Expired four days after commencement of crude liver extract.				
										Crude L. extract.	2 cc. daily	4					
	1 PP	2.4	0.95	70	35					Crude liver extract	2 cc. daily	Expired two days after commencement of treatment.					

obreviations in Table X and XI:

A.P.: Antepartum, i.e. days before delivery.
P.P.: Post partum, i.e. days since delivery.
M.T.: Malignant Tertian.
K.T.: Kahn test for syphilis.

Conclusions and Comment

From the review of the results of the present investigation, the following facts appear to be significant:

(1) Best therapeutic response to a combination of folic acid and vitamin B_{12} administered orally in E.M.F. deficiency anaemia in pregnancy.

(2) Better response to folic acid when given in combination with vitamin C during pregnancy.

(3) No difference in response to folic acid given alone or in combination with vitamin B_{12} in puerperal patients.

(4) Comparatively poorer response to crude liver extract during pregnancy and puerperium.

These findings suggest that the chief deficiency in E.M.F. deficiency anaemia in pregnancy is of folic acid with perhaps associated lesser deficiency of vitamin B_{12} and or vitamin C. They also suggest that the crude liver extract is effective only by virtue of its folic acid and vitamin B_{12} content. The less complete and slower response to crude liver extract is presumably due to its much lower folic acid content.

May, Nelson, and Salmon failed to produce megaloblastic anaemia in monkeys fed on a diet low in folic acid, unless a chronic deficiency of ascorbic acid was also present. A great deal of work is being done to solve the problem of inter-relationship of folic acid and vitamin B_{12} by several workers, VITER and his associates postulate the existence of a chain type of reaction. They state that folic acid together with unknown substances activates the formation of purine and pyrimidines from amino-acids and vitamin B_{12} probably activates the formation of nucleosides from purines and pyrimidines. According to this hypothesis both folic acid and vitamin B_{12} are bound to be required in large amounts by the growing foetus and this probably explains the relative lack of vitamin B_{12} during pregnancy as demonstrated by the better response to the combined therapy with folic acid and vitamin B_{12}, compared to the response to folic acid alone. This also explains lack of any difference in response to folic acid alone or in combination with vitamin B_{12} in the puerperal patients, as the demands for vitamin B_{12} of the growing foetus are no more to be met in the puerperal patients.

The other significant findings are:

(1) E.M.F. deficiency anaemia is generally a disease of the poor.

(2) It is much commoner in the second half of the year. The period of its maximum incidence is preceded by a quarter of relative scarcity of fresh vegetables and is associated with a period of highest incidence of gastro-intestinal disturbances like diarrhoea and dysentery.

(3) It is generally seen in its worst form in the last trimester of pregnancy.

These findings suggest that the folic acid deficiency in these cases is usually due to a combination of factors:—

(1) Diminished supply due to scarcity of vegetables.

(2) Defective absorption and deficient bio-synthesis due to gastro-intestinal upsets.

(3) Increased demands of the foetus especially during 3rd trimester which is the period of maximum foetal growth.

The deficient biosynthesis due to the altered bacterial flora of the intestines brought on by these gastro-intestinal upsets, coupled with the foetal demands, can also account for the co-existing vitamin B_{12} deficiency. Vitamin B_{12} is the growth factor of numerous bacilli and these bacteria consume vitamin B_{12} in large amounts. It has been shown that Coli Bacillus in particular has a great affinity for vitamin B_{12}. It has also been shown that this bacillus possesses a folic acid decomposing capacity as well. Although exact data concerning B_{12} metabolism in man are unknown, there is some evidence to suggest that vitamin B_{12} is synthesised by some bacteria in the intestinal tract. Denko and associates have also demonstrated that the bacteria of human intestinal tract under normal conditions can synthesise folic acid. Hence any increase in the numbers of vitamin B_{12} consuming and folic acid decomposing bacteria or any diminution in the numbers of vitamin B_{12} and or folic acid synthesising bacteria as a result of these gastro-intestinal upsets is likely to give rise to the relative deficiency of these two erythrocyte maturation factors.

This explanation for the causation of E.M.F. deficiency anaemia during pregnancy appears simple and plausible but the following findings appear to throw some doubt on this simple explanation.

(1) Throughout the 12 month period of this study, not a single case of E.M.F. deficiency anaemia was found in any non-pregnant woman inspite of the persistent and thorough search for the same amongst about 2,000 non-pregnant patients coming from the same cross-section of the population, belonging to the same socio-economic strata and subsisting on a diet similar to our pregnant patients.

(2) The slower and less complete response to folic acid during pregnancy as compared to the response during puerperium.

(3) Recurrence of anaemia in the third trimester of the subsequent pregnancy in two of these cases.

From these findings, the pregnant state itself appears to be largely responsible for the deficiency of folic acid. At this juncture it is difficult to say whether this deficiency is a true deficiency conditioned by the increased demands of the foetus, coupled with the diminished supply to the mother (due to deficient ingestion, absorption, and biosynthesis) or whether there are some other factors operating to inhibit or counteract the haemopoietic activity of folic acid. There is some evidence to suggest that certain hormones, particularly the hormones of the gonads, thyroid, adrenal cortex and anterior pituitary are concerned in the control of haematopoiesis. Castration in the male rat has been found to lower and in the female rat to raise the erythrocyte count. The administration of oestradial benzoate to castrated females caused a drop in the elevated counts while administration of testos-

terone produced a rise to normal in the castrated males. This finding demonstrates the inhibitory influence of oestrin on haematopoisis. Day et al reported an abnormal pattern for urinary hormone excretion in their patients.

The finding of marked degree of haemodilution as indicated by the excessive lowering of plasma proteins and of the specific gravity of the plasma in most of these cases supports the belief that some hormonal upset of pregnancy may be concerned in the causation of this anaemia. The lack of spontaneous remission of this anaemia even a month or more after delivery, however, (Cases Nos. 6, 20 and 21, Table XI and Case No. 5, Table II, in our previous paper) make one doubt the assumption that the pregnant state alone is entirely responsible for this anaemia. Still further investigations are required to throw more light on the exact etiology of this anaemia.

Summary

(1) Our findings in 75 cases of anaemias of pregnancy found during a twelve month period amongst the in-patients at the Daga Memorial Hospital, Nagpur, are reported and reviewed.

(2) 39 of these cases were found to be of pure E.M.F. deficiency anaemia, 19 of combined E.M.F. and iron deficiency anaemia and 17 of pure iron deficiency anaemia.

(3) All these anaemias were found to be much commoner amongst the poorer sections of the population.

(4) E.M.F. deficiency anaemia was found to be much commoner during the second half of the year. While the iron deficiency anaemia showed no seasonal variation.

(5) No particular age or parity group was found to show any special predisposition to the E.M.F. deficiency anaemia.

(6) The E.M.F. deficiency anaemia was found to be the commonest during the third trimester but it tended to appear earlier than the iron deficiency anaemia.

(7) The E.M.F. deficiency anaemia generally was of much greater severity as compared to the iron deficiency anaemia.

(8) Pre-eclampsia and various infections were found to be quite common amongst the cases of E.M.F. deficiency anaemia.

(9) Mode of onset was insidious in most of the cases of E.M.F. deficiency anaemia.

(10) Glossitis, stomatitis, diarrhoea, vomiting and anorexia, were frequently complained of by the E.M.F. deficiency anaemia cases and all these symptoms were relieved by folic acid.

(11) The incidence and degree of oedema and haemodilution was much greater in the E.M.F. deficiency anaemia cases as compared to the iron deficiency anaemia cases.

(12) No particular morphological type was found to be pathognomic of E.M.F. deficiency anaemia. Megaloblasts were not found in the peripheral blood smear and or marrow smear of every case of this anaemia.

(13) Only 3 cases out of 29 that had gastric analysis done, showed histamine fast achlorhydria

(14) Pregnant patients with E.M.F. deficiency anaemia were found to be poor obstetrical risks. The tendency to premature labour and miscarriage was very high, especially when the anaemia was of severe degree.

(16) The delivery was spontaneous and of normal duration in all cases. The average blood loss at delivery was only 4.4 ounces. There were no obstetrical complications in any of these cases.

(17) The gross maternal mortality of the E.M.F. deficiency anaemia cases was about 14%. 86% of these deaths were after delivery and only 14% were during the pregnancy. There were no deaths amongst the iron deficiency anaemia cases. The incidence of morbidity was also very high amongst the E.M.F. deficiency anaemia cases.

(18) There was a gross foetal loss of 39.6% in the E.M.F. deficiency anaemia cases There was no foetal loss due to iron deficiency anaemia.

(19) Folic acid was found to be the best haematinic for the E.M.F. deficiency anaemia.

(20) Hospitalization with absolute bed rest was considered essential for all the severe cases.

(21) Artificial termination of pregnancy is not recommended in these cases and is warned against.

(22) Full haematological investigations prior to commencement of therapy are considered absolutely essential for achieving best therapeutic results and haphazard treatment of these cases is highly deprecated. The anaemias of pregnancy, even of moderate degree, are not to be dealt with lightly. They must be put on the same footing as pre-eclampsia and given prompt and proper attention to avoid catastrophe. The cases of moderate degree appear to pass on to the severe stage fairly acutely as the pregnancy advances, especially with onset of any febrile illness, or acute bacillary dysentery. As the prognosis for both the mother and the infant is much better if the anaemia is treated in its early stages, adequate treatment of anaemia while it is still of mild or moderate degree is considered the best form of prophylaxis available at present to lower the high maternal mortality from this serious malady.

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References

1. Balfour M. I.: Ind. Med. Gaz.; 62, 491, 1927.
2. Chatterjea H. N.: Ind. Med. Gaz.; 73, 267, 1938.
3. Dasgupta C. R. & Chatterjea J. B.; Ind. Jour. Med. Res.; 37, 455, 1949.
4. Davis B. D. & Mingoli E. S.: Jour. Bact.; 60, 17. 1950.
5. Day L. A. et al: Proc. Staff Soc. Mayo Clinic; 24. 149, 1949.
6. Denko C. W., et al: Arch. Biochem.; 10 33, 1946.
7. Dyke W. J. C. & Collaborators: Lancet; P. 486, 1950.
8. Gordon A. S. & Charipper H. A.: Ann. New York Acad. Sci.; 48. 615, 1947. Quoted by Wintrobe.
9. Haslewood G. A. D. & King E. J.: Biochem. Jour.; 31, 920, 1937. Quoted by Delory G. E., in Photoelectric methods in clinical Biochemistry.
10. Horrigan D., et al: Jour. Clin. Invest.; 30, 31, 1951.
11. Kothari B. V. & Bhende Y. M.: Ind. Jour. Med. Res.; 40, 387, 1952.
12. Lajtha L. G.: Clin. Sc.; 9, 287, 1950.
13. May C. D., Nelson E. N. & Salmon R. J.: Jour. Lab. Clin. Med.; 34, 1724, 1949.
14. Mcswiney S. A.: Ind. Med. Gaz.; 62, 487, 1927.
15. Mitra D. D.: Ind. Med. Gaz.; 74, 671, 1939.
16. Najjar V. A. et al: J.A.M.A.; 126, 357, 1944.
17. Najjar V. A. & Barret R.: 'Vitamins & Hormones'; 3, 23, 1945.
18. Napier L. E. & Neal Edwards M. I.: Memo. Anaemias of Pregnancy. 1942.
19. Odland L. M. et al: Proc. Soc. Exper. Biol. & Med.; 70, 438, 1949.
20. Raj P.: 'Blood in Pregnancy' in Print Jour. Obst. & Gyn., India.
21. Raj P: Folic acid with & without Vitamin B_{12} in the treatment of macrocytic anaemia of Pregnancy. in Print. Jour. Obst. & Gyn., India.
22. Spies T. D.: Amer. Jour. Med.; 1, 473, 1946.
23. Tatum H. G.: Amer. Jour. Obst. Gyn.; 66, 27, 1953.
24. Vilter R. W., et al: Blood; 5, 695. 1950.
25. Wills L. & Collaborators: Ind. Jour Med. Res.; 17, 777, 1930.
26. Wintrobe M. M.: Clinical Haematology: Lea & Febiger. 1951.
27. Review on Haematology. Ind. Council Med. Res. special report series, No. 26, 1953.