Anaemia in Pregnancy Associated with "Big Spleen Disease"*

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Brit. med. J., 1966, 2, 548–551

We have previously reported an association between idiopathic tropical splenomegaly, lymphocytic infiltration of the hepatic sinusoids, hyperglobulinaemia, and a raised fluorescent antibody titre to malaria, and have suggested that this is due to an abnormal immune response to malaria, possibly connected with *Plasmodium malariae* infection (Gebbie *et al.*, 1964; Marsden *et al.*, 1965). This syndrome is known locally as big spleen disease, and is referred to by that title in this paper. These patients usually have a chronic anaemia due to a shortened red-cell survival (Marsden *et al.*, 1965). In one series 13 of the 15 females were pregnant or lactating (Gebbie *et al.*, 1964).

We now present clinical, haematological, biochemical, and immunological studies on a series of patients with anaemia in pregnancy associated with big spleen disease. The relation of these cases to the overall picture of anaemia in pregnancy as seen in Kampala is reported.

Materials and Methods

Of 8,579 patients attending the obstetric service of Mulago Hospital in 1964 95 (1.1%) were admitted to hospital because of anaemia, with a haemoglobin of less than 7 g./100 ml.

Detailed studies of these patients, including haemoglobin, paper electrophoresis, glucose-6-phosphate-dehydrogenase assay (Doxiadis, 1961), liver-function tests, and liver biopsy, enabled us to classify the cause of anaemia as shown in Table I.

TABLE I.—*Anaemia in Pregnancy: 95 Antenatal Cases Admitted for Anaemia in* 1964

	No. of Cases
Hookworm infestation and iron deficiency	50
Anaemia associated with big spleen disease	28
Anaemia associated with megaloblastic change and big spleen disease	1
Megaloblastic	2
Acute haemolytic with no splenomegaly and normal liver biopsy	2
Miscellaneous	12

Fifty cases of anaemia were due to iron deficiency associated with hookworm infestation. Twenty-nine had the features we consider to be associated with big spleen disease. One of these had associated sickle-cell disease and another megaloblastic erythropoiesis. There were two other cases of megaloblastic anaemia, two cases of acute haemolytic anaemia without big spleen disease, and 12 cases of anaemia in which a final diagnosis could not be made.

Fluorescent antibody titre for malaria was estimated by the method of Voller and Bray (1962), a double-blind technique with *Plasmodium falciparum* as antigen being used.

The 29 cases of big spleen disease are here reported in detail.

Clinical Presentation

The majority of these patients presented with a short history of a few days' fever, jaundice, darkened urine, and pain in the left hypochondrium from an enlarging spleen. In three the jaundice had occurred twice in the same pregnancy, and eight had noted jaundice in a previous pregnancy. Most of them complained of dyspnoea, and three noted swelling of the ankles. All were between 15 and 30 years of age, which corresponds with the normal age-distribution of admissions to the obstetric wards.

In three patients the spleen was not palpated, but minor degrees of splenomegaly can be very difficult to detect in late pregnancy. These cases were included because they showed the liver-biopsy appearances of big spleen disease. In our experience of this disease in men, and from necropsy studies, the liver changes are always associated with some splenic enlargement.

Cases occurred throughout pregnancy, but the majority presented at 30–34 weeks (Table II).

TABLE II.—*Big Spleen Disease in Pregnancy. Stage of Pregnancy at Time of Admission in 29 Cases*

Weeks of pregnancy	20–24	25–29	30–34	35–39	40
No. of cases	8	6	11	2	2

Two of these patients (6.9%) were pregnant for the first time and 24 (82.6%) had had three or more pregnancies, whereas of 2,500 consecutive normal deliveries at Mulago Hospital 25% were primigravida and 56% were gravida-3 or more (Table III).

TABLE III.—*Big Spleen Disease in Pregnancy. Number of Previous Pregnancies in 29 Cases Compared with All Deliveries at Mulago Hospital*

No. of Pregnancies	No. of Cases with Big Spleen Disease	2,500 Consecutive Normal Deliveries at the Mulago Hospital
1	2 (6·9%)	25%
2	3 (10·3%)	19%
3	7 (24·1%)	17·7%
4	6 (20·6%)	15%
5	4 (13·8%)	9·6%
6	7 (24·1%)	13·7%

Each of the 29 patients was questioned about previous pregnancies, including abortions. The total number of abortions experienced by the 29 patients expressed as a proportion of the total number of pregnancies, whether ending in abortion or delivery, was 17.3%. The similar rate for 2,500 consecutive deliveries at the Mulago Hospital was 7.3%.

The tribal distribution of patients with severe anaemia is shown in Table IV. Among cases with big spleen disease there were 39% of Banyarwanda and only 31% Baganda, the dominant tribe around Kampala, whereas among 2,500 normal deliveries in the Mulago Hospital in 1964 67% were Baganda

TABLE IV.—*Tribal Distribution of 29 Cases of Big Spleen Disease in Pregnancy Compared with All Cases of Anaemia Admitted in* 1964 *and 2,500 Consecutive Deliveries*

	All Cases of Anaemia (%)	Cases with Big Spleen Disease and Anaemia in Pregnancy (%)	Normal Deliveries (%)
Baganda	52·5	31	67
Banyarwanda	22·1	39	6
Others	25·4	30	27
Total cases	95	29	2,500

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and 6% were Banyarwanda. This difference is highly significant ($P<0.01$), and is in keeping with our earlier findings (Hamilton *et al.*, 1965).

Clinical Findings.—The main clinical findings are shown in Table V.

TABLE V.—*Clinical Findings in 29 Cases of Big Spleen Disease in Pregnancy*

		No. of Cases
Anaemia		29
Jaundice	Definite	10
	Doubtful	6
	Absent	13
Splenomegaly	5 in. (12·5 cm.) or more below costal margin	15
	< 5 in. (12·5 cm.) below costal margin	11
	Not palpable	3
Oedema of ankles		3
Liver enlarged 1–2 in. (2·5–5 cm.)		18

The jaundice never persisted for more than five days.

Clinical Course of the Condition.—Thirteen of the 29 patients presented with evidence of acute haemolysis. When it occurred the haemolysis was acute in onset and self-limiting. The following is a typical case history. A 25-year-old gravida-4 was admitted at 24 weeks with fever and splenomegaly. On admission her Hb was 10 g./100 ml. Overnight she became jaundiced and her Hb fell to 6.4 g./100 ml. Her serum bilirubin rose to 5 mg./100 ml. She had haemosiderin in the urine and methaemalbumin in her plasma. There was a reticulocyte response of 15%, and her jaundice cleared in three days. She was given antimalarial drugs, but blood transfusion was not necessary. Her haemoglobin rose slowly to 12 g./100 ml., and she went on to have a normal delivery.

Outcome of Pregnancy.—The outcome of pregnancy in these 29 cases is shown in Table VI. Unfortunately, in nine cases there is no record of the mode of delivery.

TABLE VI.—*Big Spleen Disease in Pregnancy. Result of Pregnancy in 29 Cases*

	No. of Cases		No. of Cases
Full-term normal delivery	9	Stillbirth	3
Premature	4	Abortion	3
Twins	1	No record	9

Investigations

Pathology.—The changes seen on liver biopsy have been fully described elsewhere (Marsden *et al.*, 1965). They consist essentially in lymphocytic infiltration of the sinusoids of the liver with a varying degree of Kupffer-cell hyperplasia; there is little or no malarial pigment. The parenchymal cells are usually normal (Fig. 1). All 29 cases showed these changes to a varying degree.

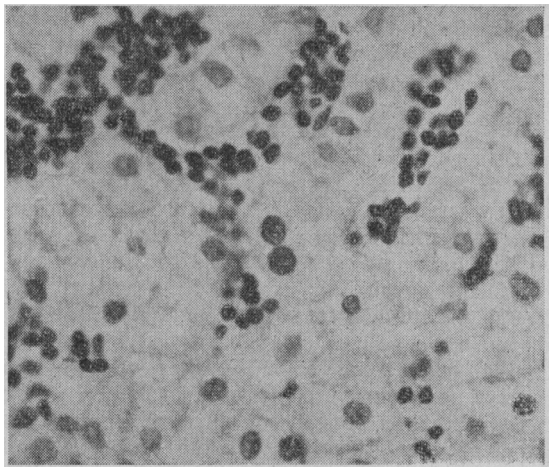

FIG. 1.—Infiltration of liver sinusoids by lymphocytes. (H. and E.)

Haematology on Admission.—The results of standard haematological tests are shown in Table VII. The raised reticulocyte count and hyperplastic normoblastic marrows are consistent with a haemolytic process. In addition, methaemalbumin was present in three cases which also had haemosiderin in the urine. Fourteen cases had iron deficiency, as judged by a low M.C.H.C., in addition to the anaemia of big spleen disease. There is evidence of acute haemolysis in 13 cases with rapidly developing anaemia, acholuric jaundice, and/or a high reticulocytosis. The Coombs tests were negative in all cases. Twenty-eight patients had AA haemoglobin and one SS on electrophoresis. The tests for glucose-6-phosphate-dehydrogenase were all normal; in six cases with acute haemolysis the test was repeated several months after the acute haemolytic episode, when the reticulocyte counts had returned to normal, and no deficiency was found. By this test we detected no homozygous or hemizygous cases of glucose-6-phosphate-dehydrogenase deficiency, but we did not examine for heterozygotes. Ten of the 29 patients had a raised serum bilirubin. The alkaline phosphatase, thymol turbidity, serum transaminases, and bromsulphalein clearances were all normal, confirming the absence of hepatic parenchymal-cell disease. As previously reported, there was a slight rise in γ-globulin. β_2-macroglobulins were detected in all cases. Detailed studies on these plasma protein abnormalities will be reported separately. Thirteen patients had an excess of urobilinogen in the urine, and in three haemosiderin was detected.

TABLE VII.—*Big Spleen Disease in Pregnancy. Haematological Findings on Admission in 29 Cases*

	Mean	Range
Hb	5·1 g./100 ml.	(2–7 g./100 ml.)
P.C.V.	19·9%	(12–27%)
M.C.H.C.	28·6%	(20–38%)
Reticulocytes	8·6%	(1–24%)

Bone-marrow: megaloblastic, 1; normoblastic hyperplasia, 24; no record, 4.

Malaria Studies

Malaria Parasites.—In two patients a heavy infection with *P. falciparum* was found on admission, and in three others a light infection with *P. malariae.* Detailed studies were vitiated by the therapeutic use of antimalarial drugs.

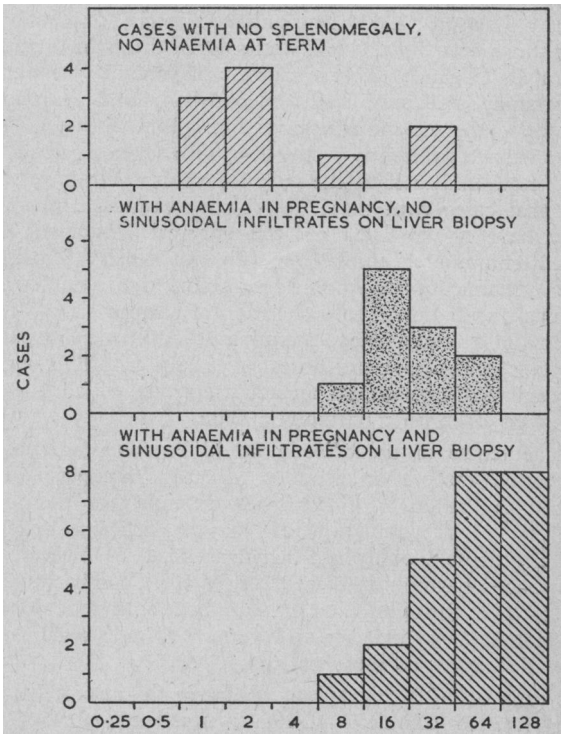

FIG. 2.—Fluorescent antibody titres for malaria.

Malaria Antibodies.—Antibody titres were estimated by a double-blind technique on three groups of patients: (*a*) those with normal haemoglobin at term and no splenomegaly, (*b*) those with a severe anaemia and no splenomegaly but with normal liver biopsies, and (*c*) those with big spleen disease. The results are shown in Fig. 2. The titres of patients without anaemia followed a normal log distribution curve, but both the other groups showed raised titres. Comparison of the cases with the normal group gives a highly significant correlation between high antibody titres and sinusoidal infiltrates in the liver ($P<0.01$). However, the group with severe anaemia but no big spleen disease on liver biopsy fell between these two, and is not significantly different from either. The raised antibody titre in this group without big spleen disease suggests that malaria itself plays a part in the production of anaemia of pregnancy in Kampala.

Therapy

As a result of our earlier experience when we found a high incidence of *P. malariae* in cases of big spleen disease, and because of the danger of recurrent acute haemolytic attacks, these cases have been given a 15-day course of 15 mg. of primaquine daily coupled with a curative course of chloroquine for three days and weekly prophylaxis with 300 mg. of chloroquine. Treatment was started either empirically or on receipt of the liver biopsy result. No patient on this regimen has had a recurrence of acute haemolysis. Two of the patients became pregnant again in 1965. Both were given antimalarial drugs throughout pregnancy. They have had no further haemolytic episodes, and delivered normal children at term.

Glucose-6-phosphate-dehydrogenase deficiency is common around Kampala, but we have seen no cases of acute haemolytic anaemia due to this drug. Kellermeyer *et al.* (1962) have shown that patients with glucose-6-phosphate-dehydrogenase deficiency taking 15 mg. of primaquine daily may have a mild transient anaemia which is not dangerous.

Discussion

In the tropics haemolytic anaemia in pregnancy has been noted by Lawson (1962) in Ibadan (Nigeria) to occur only among those who did not take antimalarial drugs in pregnancy. In Kampala (Uganda) there is a group of patients with anaemia of pregnancy associated with splenomegaly and lymphocytic infiltrates in the hepatic sinusoids (big spleen disease). These patients behave differently from those with severe anaemia, who do not show infiltrates in the liver sinusoids. We have shown earlier that cases with these liver-biopsy changes and splenomegaly have a shortened red-cell survival (Marsden *et al.*, 1965; Richmond *et al.*, 1966). In this series 13 pregnant patients presented with acholuric jaundice, high reticulocytosis, and an acute self-limiting exacerbation of haemolysis. We have not seen similar acute episodes among 90 non-pregnant patients with big spleen disease and no other condition. This suggests that pregnancy precipitates an acute episode which is superimposed on a chronic haemolytic state.

The acuteness of the episode would be consistent with an autoimmune mechanism, sudden marrow hypoplasia, as is described in the crisis of sickle-cell anaemia; or the sudden haemolysis of a population of enzyme deficient cells—for example, glucose-6-phosphate-dehydrogenase. However, antibody-induced haemolysis is unlikely, as the Coombs tests were all negative; the presence of jaundice and reticulocytosis excludes marrow hypoplasia, and we have found no evidence of enzyme deficiency in these patients.

The association of big spleen disease with malaria has been already reported (Gebbie *et al.*, 1964; Marsden *et al.*, 1965), and is borne out by the high antibody titres in this series. Unfortunately, detailed studies of malaria parasites in these patients have been invalidated by the use of antimalarial drugs, but earlier work suggests that there is a relation between this syndrome and *P. malariae* (Marsden *et al.*, 1965). *P. malariae* is an organism difficult to identify owing to its low density of parasitaemia, and is renowned for the chronicity of its exo-erythrocyte cycle. The distribution of cases of big spleen disease follows closely the distribution of malaria in Uganda (Hamilton *et al.*, 1965) and does not seem to occur in the non-malarious areas.

It is too early as yet to draw conclusions from the results of treatment, but two patients attending a long-term therapeutic trial of antimalarial drugs in big spleen disease have shown regression of their splenic mass and an absence of haemolytic attacks in subsequent pregnancies. The effect of antimalarial drugs in our cases and in those from West Africa suggests that the precipitating factor may be an acute attack of malaria. We have direct evidence of this in only two cases when heavy *P. falciparum* infections were found on admission. The best response to treatment has been in those cases with spleens which were found to be small or acutely enlarging. In those with chronic splenomegaly the spleen has not decreased in size. This suggests that these cases may have reached a chronic stage, with marked irreversible, pathological, and haemodynamic changes in their portal circulation. The haemodynamic aspects of these cases have been fully reported elsewhere (Williams *et al.*, 1966).

The very high tribal incidence among the Banyarwanda group is striking. These people are immigrants to Buganda from Rwanda and Burundi, where there is far less malaria. It is tempting to suggest that big spleen disease in these cases is due to a lack of immunity developed in early life; however, many of the Banyarwanda patients were born and bred in Buganda. These people also represent a very poor section of the community, and we have not yet seen a case of big spleen disease among the wealthy members of society.

The danger of this condition to the foetus is considerable, as is shown by the very high abortion rate (17.3%). During the acute haemolysis the oxygen-carrying power of the blood is dramatically reduced, and it is reasonable to postulate that this leads to abortion or foetal death *in utero*. In addition, severe sudden anaemia is dangerous to the mother. In the period 1958–61 at Mulago Hospital, Kampala, there were 95 maternal deaths, of which 12 were attributed to anaemia. Necropsy material was available for review in five cases, and two of these showed sinusoidal infiltrates and both had increased spleen weights (Rendle Short, 1962).

Conclusion

There are in Kampala, and probably elsewhere in the tropics, a group of patients with splenomegaly, lymphocytic sinusoidal infiltrates in the liver, and raised antibody titres for malaria (big spleen disease). These patients have a chronic low-grade haemolytic anaemia which predisposes them to acute self-limiting haemolytic episodes of anaemia in pregnancy. The factor or factors precipitating these attacks are not clear, and acute haemolytic episodes are not seen in all pregnancies. These attacks constitute a danger to the foetus and the mother. The syndrome can be differentiated by liver biopsy from other causes of anaemia of pregnancy with which it may coexist. We believe that this syndrome is possibly an abnormal immune response to malaria, and that these cases should be treated by a full 15-day course of 15 mg. of primaquine daily to eradicate the infection coupled with a curative course of chloroquine and followed by prolonged chemoprophylaxis against malaria throughout pregnancy and in all future pregnancies.

Summary

Of 95 cases of severe anaemia of pregnancy (Hb<7 g./100 ml.) admitted to the Mulago Hospital, Kampala, in 1964 29

cases were found to have lymphocytic infiltrates in the hepatic sinusoids on liver biopsy and a significantly raised antibody titre for malaria, and 26 of the 29 had palpable splenomegaly. This syndrome is called locally big spleen disease. These 29 cases constitute a special group, and are described in detail.

Thirteen patients presented with acute haemolytic episodes shown by acholuric jaundice and high reticulocyte counts. Such acute episodes have not been seen in 90 non-pregnant cases with this syndrome.

Non-pregnant cases have all been shown to have a shortened red-cell survival of varying degrees. It is concluded that the pregnant patients have a chronic low-grade haemolytic process which predisposes them to acute haemolytic episodes during pregnancy. The possible factors producing these acute attacks and the danger to the mother and foetus are discussed.

Big spleen disease is believed to be an abnormal immune response to malaria. It should be suspected when splenomegaly is found, and can be diagnosed by liver biopsy. Pregnant women with this condition with or without anaemia should be treated with a course of 15 mg. of primaquine daily for 15 days coupled with a curative course of chloroquine and followed by prolonged chemoprophylaxis against malaria throughout pregnancy and in all subsequent pregnancies.

We are grateful to Professors J. A. Tulloch, R. R. Trussell, and A. W. Woodruff, and Drs. J. Richmond and G. Cook, for their encouragement and criticism. Financial support was provided by the Leverhulme Trust, the World Health Organization, and the U.S. Army Medical Research and Development Command, Department of the Army, under Research grant number DA-MD-49-193-63-6101.

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Chronic Enteric Carriers: Management of Personal Problems*

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Brit. med. J., 1966, **2**, 551–555

The enteric fevers (typhoid and paratyphoid A, B, and C) have been known to man for many centuries, although it is comparatively recently only that their incidence has decreased in lands with high standards of sanitation. In Western Europe, however, epidemics still occur, usually when the basic principles of hygiene have been lowered in association with direct or indirect contamination of food or water-supplies by a carrier. During the past 30 years such notable epidemics of typhoid have occurred in Bournemouth in 1936, Croydon in 1937, Zermatt in 1963, and Aberdeen in 1964. In 1963 there were simultaneous outbreaks of paratyphoid B in East Anglia, Surrey, Yorkshire, and the Edinburgh area, with frozen Chinese egg as the common source of infection (*Brit. med. J.*, 1963). Paratyphoid A and C seldom occur primarily in the United Kingdom, being almost invariably imported from other lands.

According to Leff (1957), about 10% of all convalescent typhoid patients excrete typhoid bacilli for three months after infection, with 2 to 5% becoming chronic carriers. In Edinburgh in 1963 11 (5.8%) out of 188 persons infected were still excreting *Salmonella paratyphi B* after three months (Sharp *et al.*, 1964), of whom six (3.2%) became chronic carriers. Of the two types of enteric carrier the faecal excreter is more common than the urinary excreter. The chronic carrier state may be predisposed to by pre-existing gall-bladder or renal infection, but may also follow acute cholecystitis or pyelitis as a complication of enteric fever. In some instances, also, a person may become a chronic carrier without any relevant past history. Surgical removal of the gall-bladder or kidney is not always successful in curing the chronic carrier state. Numerous claims have also been made periodically about the efficacy of various antibiotics, of which only long-term ampicillin has given encouraging results to date (Christie, 1964). When a permanent medical or surgical cure becomes available the carrier problem may not necessarily be completely resolved. Many carriers, disappointed by previous failures and in good general health, may be unwilling to undergo further treatment, even if this does not involve surgery and its attendant risks. Medical problems may present in toxic reactions to antibiotics, while social problems may be associated with prolonged absence from the home or work. There may be additional surgical problems with carriers who have multiple foci of infection of the biliary or urinary tracts, requiring excessively radical measures.

Carriers employed as food-handlers can be legally excluded from this occupation (*Statutory Instrument*, 1959). These measures are necessary to safeguard the public health, but such carriers are faced with the problem of finding other employment and learning new trades, often in middle or later life. However, as many carriers are women, food-handling does not end there, but continues in the home, where families may have to be fed. Difficulties may arise with individuals in achieving a balance between periodical supervision and the emphasizing of personal hygiene, with the potential danger of creating "leper neuroses." Involvement of the central nervous system, and varying degrees of mental confusion and apathy, are not uncommon clinical features of enteric fever, which in some cases may have residual effects in post-enteric psychoses and allied states. These have been known to persist for some months, although views differ on whether mental recovery is thereafter complete or not. Such persons who continue to excrete the organism may readily become permanently neurotic.

* This paper, under the title of "Chronic Enteric Carriers, their Problems and Public Health Management," was awarded the Littlejohn Gairdner Prize Essay.

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