Subject 2

The initial maximal gastric output in the patient with a chronic duodenal ulcer was high (40 mEq/hr.). One week later the response to the same stimulus was reduced, as was the response to augmented histamine stimulation (see Chart and Table III). In the interval between the two tests there had been no change in diet or ingestion of alcohol, salicylate, etc. The patient, who initially complained of symptoms typical of duodenal ulceration, became asymptomatic at the time of his later tests.

TABLE III.—*Results in Subject 2*

Route	Dose	Peak Hourly Acid Output (mEq/hour)		
		Series 1	Series 2	% Reduction
Pentagastrin: intramuscular	6 μg./kg.	42·09 40·07	5·7	73
Augmented histamine test: subcutaneous	40 μg./kg.	— —	5·2 3·7	

Discussion

In Subject 1, following five tests in which gastric secretion was stimulated by pentagastrin, with consistent reproducible results in the normal range, the secretory response of the stomach underwent a qualitative change which consisted of a decrease in basal acid secretion and a decrease in maximal acid response to all gastric stimulants used. The output of pepsin also decreased, though not as markedly as acid.

The impairment of the response to all stimulants suggested that the decreased gastric responsiveness was not selective and was not due to an immunological reaction to pentagastrin. It seemed probable that the impaired gastric secretion was either due to severe damage of the gastric mucosa (Hubel, 1966; Rohrer and Welsh, 1967) or that the stomach had become unresponsive to stimulants, as reported in patients with normal peptic mucosa and pancreatic adenomata, who showed markedly impaired secretory response, some of which could be reversed by treatment with steroids (Hindle *et al.*, 1964). The former cause seems more probable in Subject 1 of this study, since a gastric biopsy showed severe mucosal damage and parietal cell loss. Unfortunately no information is available about the histology of the stomach during the initial five tests, but the stomach was then functionally normal. Histological evidence of comparative sparing of the chief cells is compatible with the smaller reduction in pepsin output compared with acid. It seemed probable that the low acid output in the tests of series 2 was due to decrease in the number of parietal cells and not due to secretion and subsequent transmucosal loss of acid in view of the failure to demonstrate back diffusion of acid.

The presence of antibodies to parietal cells in Subject 1 does not, unfortunately, solve the problem of whether parietal cell damage precedes or follows the appearance of antibodies, since six months had elapsed between the change in secretory pattern and the antibody determination.

Significant impairment of the gastric secretory response to stimulants of the type noted in this study has not been reported previously, though the converse type of response has been noted with low acid output in response to stimulants followed later by greater acid output (Weir, 1967).

Gastric testing by methods in current use has been shown to produce results which are reproducible on repeated testing (Wormsley *et al.*, 1967; Jepson *et al.*, 1968). Indeed, this is one of the most important assumptions on which tests of gastric function are based. This study, however, has shown that the gastric response to stimulants can alter qualitatively over a period of time, and this type of reaction must be borne in mind, particularly when the assessment of gastric function depends on comparison of response to repeated stimulation—for example, after operation such as vagotomy.

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Severe Haemolytic Anaemia in Pregnancy in Nigerians Treated with Prednisolone

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Summary: Haemolytic anaemia of obscure aetiology is a common complication of pregnancy in Nigeria. Treatment with antimalarials and folic acid is usually followed by a rapid remission, but response is slow in about 25% of patients and haemolysis continues uncontrolled in about 5%. The administration of prednisolone to six patients with uncontrolled haemolysis was followed by rapid recovery in five and possible benefit in one. Risks of prednisolone therapy to the mother appear to be slight and outweighed by the risks of continued severe anaemia and frequent blood transfusions. There seemed to be no appreciable increase of fetal loss compared with that in anaemic pregnancies not treated with prednisolone.

Introduction

Severe anaemia in pregnancy is a major problem in obstetric practice in West Africa, and about 250 pregnant or recently delivered patients are seen each year at University College Hospital, Ibadan, Nigeria, with packed cell volume (P.C.V.) 23% or less. The aetiology of anaemia is complex, but two factors, haemolysis and folate deficiency, stand out as being of prime importance (Edozien *et al.*, 1961; Lawson, 1962). Folate

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deficiency is the result of poor nutrition, the demands of pregnancy, and the high requirements of active erythropoiesis in patients with haemolytic disease. The cause of haemolysis is more obscure, and several factors contribute. The administration of malaria prophylactics throughout pregnancy largely prevents anaemia (Lawson, 1962), and it has been inferred that one important cause of haemolysis is malaria following the reduction of immunity during pregnancy (Bruce-Chwatt, 1952).

The administration of antimalarials and folic acid is followed by a rapid rise of the haematocrit in most anaemic pregnant patients, but response is slow in about 25%, and in about 5% of patients the P.C.V. continues to fall in spite of therapy. Persistent haemolysis has an association with the "tropical splenomegaly syndrome" (*British Medical Journal*, 1967), but the relation to massive splenomegaly is not absolute (Hamilton *et al.*, 1966).

Our purpose is to report six pregnant Nigerian women in whom severe haemolysis persisted after the elimination of malaria and to discuss aetiology and therapy, with special reference to the synthetic corticosteroid prednisolone.

Material and Methods

Haematological Methods

Haematological techniques were as described by Dacie and Lewis (1963). The haemoglobin (Hb) concentration was estimated by the cyanmethaemoglobin method and the packed cell volume by the Hawksley microhaematocrit. The reticulocytes were counted in 1,000 cells stained with brilliant cresyl blue, the results being expressed as the reticulocyte index (R.I.) calculated from the formula R.I. = retic.% × P.C.V./45. The R.I. was recorded as normal (<1·9), moderately raised (2–3·9), and high (>4).

Bone marrows were collected from the iliac crest, and smears made and stained with May–Grunwald and the Giemsa stain. Marrows with no morphological abnormalities or with only slight changes towards megaloblastosis or occasional giant metamyelocytes were classified as essentially normoblastic. Other specimens were classified as essentially megaloblastic or grossly megaloblastic.

Serum folate activity was assayed with *Lactobacillus casei* as the test organism (Waters and Mollin, 1961). The range of normal was taken to be 5–30 ng./ml. (Fleming, 1968b). Serum vitamin B_{12} concentrations were assayed with *Lact. leichmanii* as the test organism ; the normal range in Nigerians is 160–2,125 pg./ml. (Fleming, 1968a).

Red Cell Survival.—Red cell survival was studied in one patient by labelling her own cells with hexavalent sodium chromate (^{51}Cr) as described by Dacie and Lewis (1963). An Ekco Annular Scintillation Counter and an Ekco Automatic Scaler were used for counting blood samples ; surface counting was performed with Labgear Directional Scintillation Counter and Labgear Clinical Ratemeter.

Treatment and Progress of Patients

Patients were assessed by the obstetrician on duty regarding the necessity for blood transfusion. As a general rule patients with P.C.V. 14–17% received a packed cell transfusion of 500 ml., while patients with a P.C.V. of 13% or less received an exchange blood transfusion by the method described by Fullerton and Turner (1962). If the P.C.V. fell subsequently to 17% it was usual to give 500 ml. of packed cells.

From the day of admission patients received chloroquine 800 mg., pyrimethamine (Daraprim) 25 mg./week, ferrous sulphate (Fersolate) 200 mg., vitamin B (Becosym) 1 tablet, and ascorbic acid 50 mg. three times per day. Bone marrow biopsy was performed either on the first or second day after admission and folic acid 5 mg. three times per day was given as soon as the specimen had been collected. When an exchange blood transfusion was given the patients received tetracycline 1,000 mg./day in four divided doses for five days. Other treatments were given as indicated.

The P.C.V. was estimated every day, and the reticulocytes were counted on alternate days. It was the aim to keep the patients in hospital until they were in no possible danger from anaemia, and to discharge them to the antenatal or postnatal clinic, usually when the P.C.V. was constantly 25% or above.

Haematocrit Response in the First 10 Days.—The P.C.V. on the second post-transfusion day was the baseline from which the P.C.V. was judged to rise or fall, and the haematocrit response classified as: (1) P.C.V. rising, when there was a rise of 3% from the baseline that was maintained ; (2) P.C.V. falling, when there was a fall of 3% from the baseline ; and (3) P.C.V. steady, when the P.C.V. remained within 2% of the baseline during the first 10 days of treatment.

Steroid Therapy

Prednisolone was given—20 mg. three times a day for one week, 15 mg. three times a day for one week, and 10 mg. three times a day as maintenance dose—to certain patients in whom the P.C.V. could not be maintained without numerous blood transfusions.

Patients Studied

The patients were selected from 151 consecutive pregnant Nigerians admitted to University College Hospital, Ibadan, with a P.C.V. of 23% or less. It was not possible to assess the haematocrit response to treatment in 41 patients, as they had received treatment before admission or had delivered, defaulted, or died during the first 10 days of treatment. The P.C.V. rose rapidly in 70 of the remaining 110 patients, remained within 2% of the baseline in 33, and continued to fall in 7 in spite of treatment. Steroid therapy was tried in six patients with apparent intractable haemolysis.

Results

All six patients with severe haemolysis in pregnancy were illiterate Yorubas living in or near Ibadan. Five presented at the outpatient department complaining of breathlessness, and one was referred by another hospital for treatment of her severe anaemia. Two were primiparous and four had had between

Details of Six Pregnant Nigerians with Haemolytic Anaemias Treated with Prednisolone

Case No.	Parity	Previous Anaemia	Gestation (Weeks)	Spleen (cm.)	Liver (cm.)	Jaundice	Raised J.V.P.	P.C.V. %	R.I.	S.F.A. (ng./ml.)	Serum B_{12} (pg./ml.)	Hb Electrophoresis	Marrow	No. of Blood Transfusions	Hb (g./100 ml.)	
															At Delivery	4 Weeks Postpartum
1	2	+	22	11	8	+	−	12	4·8	N.R.	175	AA	Meg.	7	12·5	13·6
2	2	−	32	4	4	+	+	8	0·6	3·6	200	AA	Gross meg.	5	13·6	14·5
3	5	−	24	0	4	−	+	13	11·5	N.R.	N.R.	AS	Norm.	4	12·0	12·8
4	1	−	28	0	0	−	+	8	0·8	1·0	450	AA	Meg.	4	13·3	14·0
5	0	−	24	12	8	−	−	14	N.R.	1·2	N.R.	AA	Norm.	4	6·8	Defaulted
6	0	−	20	12	6	+	−	12	N.R.	5·0	425	AA	Meg.	4	Defaulted	Defaulted

Gross meg. = Grossly megaloblastic. J.V.P. = Jugular venous pressure. Meg. = Essentially megaloblastic. Norm. = Essentially normoblastic. N.R. = Not recorded. P.C.V. = Packed cell volume. R.I. = Reticulocyte index. S.F.A. = Serum folate activity.

one and five previous pregnancies (see Table). Past history was unremarkable, except that Case 1 had been treated at University College Hospital, Ibadan, for severe anaemia during a previous pregnancy. All had severe pallor of the mucosal membranes and three were clinically jaundiced; skin pigmentation was normal. There was distension of the jugular veins above the sternal angle of three patients when they were reclining at 45°. None showed oedema. Four were judged to be in the second trimester and two to be in the third trimester of pregnancy. One patient had moderate splenomegaly and three had gross splenomegaly (>10 cm. below the costal margin); five had palpable livers.

Haematology

The P.C.V. on admission was between 8 and 14%; the red cells were normochromic and showed great anisocytosis and polychromasia; nucleated red cells were present in the peripheral blood with increasing frequency in the severest anaemias. None were observed to have malarial parasitaemia at the time of admission. The R.I. was not estimated in two patients; it was normal in two, both of whom had megaloblastic erythropoiesis, and raised in two. The serum folate activity was low or at the lower limit of normal in four patients in whom it was estimated. The serum vitamin B_{12} was normal in four patients in whom it was measured. One patient had sickle-cell trait, but the other five patients had a normal haemoglobin electrophoretic pattern. Two patients had essentially normablastic, three essentially megaloblastic, and one gross megaloblastic erythropoiesis.

Initial Treatment and Response

All six patients received exchange blood transfusion soon after admission. There was a reticulocyte response following folic acid therapy in Cases 1, 2, 4, and 6 with megaloblastic erythropoiesis. The P.C.V. rose briefly in Cases 2 and 6, but then fell again; it fell continuously in the other four patients. All patients needed at least three further blood transfusions to maintain the P.C.V. above 18% during the first two weeks of treatment. The P.C.V. fell rapidly to 12% on the third day after exchange blood transfusion in Case 4, and she received a second exchange blood transfusion. Case 1 needed seven transfusions in all, and she is described in detail. The R.I. remained high in four patients, but in two it was depressed, probably by the frequent blood transfusions.

Response to Prednisolone

The P.C.V. rose dramatically at a rate of about 1% per day in five patients (Cases 1 to 5) from the day after starting treatment. Four out of the five maintained this improvement and reached normal Hb and P.C.V. values after about three weeks, and all had Hb of 12 g./100 ml. or more at the time of delivery (see Table), having received prednisolone for from 32 to 56 days. (Case 3 defaulted for three weeks, during which time she received no treatment.) Prednisolone therapy was delayed in Case 5 until 12 weeks after her first admission; the P.C.V. rose from 18% to 22% (Hb 6·8 g./100 ml.) on the fifth day, when she delivered spontaneously. The P.C.V. continued to rise, reaching 32% eight days after delivery, when she was discharged from hospital and was not seen again.

Prednisolone was begun in the sixth patient after her fourth blood transfusion, but there was no rapid improvement as seen in the other five patients. The P.C.V. was maintained at a post-transfusion level of 25% and she needed no further blood transfusions before being discharged from hospital after two weeks. She did not attend the antenatal clinic as instructed, but was seen again at about 36 weeks' gestation, when her Hb was 11·3 g./100 ml. She defaulted again, and it was estimated that she had received prednisolone at most over a period of five weeks.

Maternal and Fetal Results

None of the six patients was seen to have complications attributable to steroid therapy. Two (Cases 3 and 5) stopped their therapy abruptly, but were seen again three or more weeks later, and had not suffered Addisonian crises; it may be presumed that they had stopped taking pyrimethamine at the same time, but they did not complain of fever attributable to acute malaria. Steroids were reduced and finally stopped after delivery in Cases 1 to 4, and all were well when seen at the postnatal clinic.

Four infants were normal, estimated to be at 37–40 weeks' gestation, and weighed over 2,500 g. at birth. Case 2 was delivered at 37 weeks' gestation of a macerated stillborn infant weighing 1,474 g., probably the result of intrauterine anoxia at the time when the maternal P.C.V. was 8%. The outcome of pregnancy in Case 6 was not known.

Case 1

Social, Medical, and Obstetric History.—This patient was an illiterate Yoruba woman, wife of a cocoa farmer from a village near Ibadan. She gave no history of serious illness before admission except for a megaloblastic anaemia in one previous pregnancy. She had been pregnant in 1959, but had no living child from this, and no other reliable information was given.

Previous Observed Pregnancy

In March 1962 she was admitted to University College Hospital as an emergency case for treatment of anaemia. She was 30 weeks pregnant; the liver and spleen were 5 cm. below the costal margins; the jugular venous pressure was not raised.

Investigations.—Hb 2·9 g./100 ml.; P.C.V. 9%; M.C.H.C. 32%: red cells, normochromic, anisocytosis, nucleated R.B.C.s, no malarial parasites; Hb electrophoresis, AA; marrow, megaloblastic, giant metamyelocytes+, intracellular iron++; stool, scanty hookworm ova; urobilinogen, no excess detected.

Treatment and Progress.—She was given an exchange blood transfusion (E.B.T.), and shortly afterwards delivered a macerated stillborn infant. Tetracycline, chloroquine, and folic acid were given in normal dosage, but in spite of treatment the P.C.V. fell to 15% on the seventh day. She required two transfusions of 500 ml. of packed cells to raise the P.C.V. to 23%. On the twelfth day it fell again to 19%. At this time the reticulocytes were found to be 22% (R.I. 9·3). She was treated with bephenium hydroxynaphthoate (Alcopar) because of her scanty hookworm load. The P.C.V. on the eighteenth day was 22%; she was now discharged to the postnatal clinic, but defaulted.

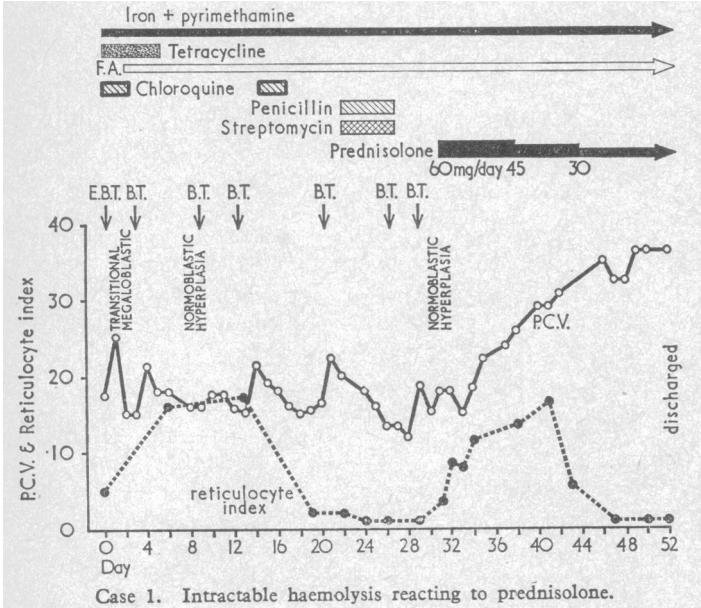
Present Pregnancy

The patient was admitted on 13 January 1963 with anaemia in pregnancy. She had received no treatment before admission and was 22 weeks pregnant; the liver was 8 cm. and the spleen 11 cm. below the costal margins. She was not in labour. The jugular venous pressure was not raised, and her temperature was 99·6° F. (37·6° C.).

Haematological examination (Fig. 1) showed: Hb 3·3 g./100 ml.; P.C.V. 12%; M.C.H.C. 28%; reticulocytes 18%; R.I. 4·8; red cells, normochromic, anisocytosis, polychromasia, nucleated R.B.C.s; W.B.C.s, normal except for an excess of metamyelocytes; blood group, B Rh-positive; Hb electrophoresis, AA; marrow, transitional megaloblastic, giant metamyelocytes +, intracellular iron +; serum vitamin B_{12} 175 pg./ml.; urobilinogen, excess detected for four days after admission; direct Coombs test, negative; stool, scanty hookworm ova; red cell survival, $T\frac{1}{2}$ ^{51}Cr (own cells) 3·4 days; surface counting showed a rising ratio of radioactivity over spleen to heart and liver to heart.

Treatment and Progress (Fig. 1).—The P.C.V. was 24% the day after exchange blood transfusion. Treatment with iron, vitamins, ascorbic acid, pyrimethamine, chloroquine, and folic acid (F.A.) was given in standard dosage. On the second and third days the P.C.V. had fallen to 15%. Packed cells 500 ml. raised the P.C.V. to 21%,

but in spite of a vigorous reticulocyte response over and above the already high reticulocyte level the P.C.V. continued to fall and the patient received in all seven blood transfusions (B.T.) in 30 days. She had an irregular high temperature from the twelfth to the twentieth day, which may have been partly due to the numerous blood transfusions. She received a further course of chloroquine and also streptomycin and penicillin. The reticulocytes were low from the 18th to the 30th day—probably the result of repeated transfusions. The bone marrow was examined twice (days 9 and 30) and found to be normoblastic and hyperplastic.



Case 1. Intractable haemolysis reacting to prednisolone.

It was decided that the continuing anaemia was due to haemolysis and a therapeutic trial of steroids was justified. Prednisolone 20 mg. three times per day by mouth was given, starting on the 31st day. There was dramatic improvement from the second day of treatment, and in five days the P.C.V. rose from 15% to 26%. Dosage was reduced to 15 mg. three times per day after one week, and 10 mg. three times per day after another week. The patient was maintained on this dose throughout pregnancy. The improvement continued and the P.C.V. reached a steady level around 35% on the 19th day. There had been a brisk reticulocytosis reaching a maximum of 25% (R.I. 16·5) on the ninth day from the starting of steroids, after which the reticulocytes fell to normal levels. The patient went to term and delivered a normal infant. After delivery she was weaned off steroids, and remained without anaemia. The haemoglobin was 13·6 g./100 ml. four weeks after delivery, after which the patient was not seen again.

Discussion

Haemolysis during *Plasmodium falciparum* infection is always in excess of the red cell destruction from rupture by the malaria parasites (Zuckerman, 1966), and a review of publications suggests a hypothesis to explain this haemolytic process (Dixon, 1966). An initial infection by malaria is followed by hyperplasia of the lymphoid tissue and the macrophages of the reticuloendothelial system (Taliaferro and Mulligan, 1937). This is accompanied by the production of antibodies, which may be demonstrated by fluorescent and haemagglutinating techniques; these are probably IgM globulins, and are not necessarily protective (Voller and Bray, 1962; Gebbie *et al.*, 1964; McGregor, 1965; Goodman, 1966; Mahoney *et al.*, 1966; Stavitsky, 1966). Other antibodies are formed which are complement-fixing, may be demonstrated by fluorescent antibody techniques, and are IgG antibodies; these include antibodies which confer some protection against further infection by acting on the late asexual forms of the parasite cycle (Cohen *et al.*, 1961; Edozien *et al.*, 1962; McGregor, 1965; D'Antonio *et al.*, 1966; Garnham, 1966; Mahoney *et al.*, 1966; Sadun *et al.*, 1966; Stavitsky, 1966).

A soluble antigen is released into the serum at schizogeny (Eaton, 1939; Cox, 1966; McGregor *et al.*, 1968) and an antigen-antibody complex is formed which is adsorbed on to both parasitized and unparasitized red blood cells, with the fixation of complement (Voller and Bray, 1962; Cooper and Fogel, 1966; Cox, 1966; Dixon, 1966; Fogel *et al.*, 1966; Zuckerman, 1966). The fixation of complement may account for the occasional reports of positive direct Coombs reactions (Vandepitte, 1949; Zoutendyk and Gear, 1951; Demirağ and Sözer, 1956; Hilton and Owen, 1963; Adner *et al.*, 1968), which are of a non-γ-globulin type (Fleming *et al.*, 1969). The "opsonized" red blood cells are phagocytosed in large numbers by the macrophages (Taliaferro and Mulligan, 1937; Dixon, 1966; George *et al.*, 1966; Zuckerman, 1966). There is a balance in the immune adult between repeated malarial infection and elimination of the asexual forms of parasite, accompanied by constant low-grade haemolysis and compensating erythroid hyperplasia.

The hyperplasia of the reticuloendothelial system in some patients leads to gross splenomegaly (tropical splenomegaly syndrome), with the secondary effects of hypersplenism, including phagocytosis of all formed elements of the blood and hypervolaemia (Gebbie *et al.*, 1964; Pryor, 1967). Two causes of haemolysis (hypersplenism and the immune fixation of complement by red cells) are not mutually exclusive (George *et al.*, 1966; Zuckerman, 1966).

The balance between infection and elimination, and haemolysis and erythroid hyperplasia, will be disturbed during pregnancy, when there is decreased resistance to malaria (Bruce-Chwatt, 1952). The consequent parasitaemia can be both prevented and treated successfully with antimalarial drugs (Lawson, 1962). Anaemia can also be prevented or treated successfully with antimalarials in most patients. The haematological picture is frequently complicated by megaloblastic erythropoiesis, which responds to folic acid (Fleming *et al.*, 1968), and in some cases the anaemia will appear to be more severe because of concurrent hypovolaemia. In a small proportion, about 5% in the present series, severe haemolysis continues in spite of suppression of malaria and the administration of folic acid, and the patients need repeated blood transfusions, or the administration of prednisolone, to maintain the P.C.V. above 18%.

It is possible only to speculate on the cause of continued haemolysis, but it could be explained in an extension of the above hypothesis if a soluble serum antigen, or antigen-antibody complex, persisted after the elimination of *P. falciparum*. The soluble antigen demonstrated by McGregor *et al.* (1968) in the serum of children and pregnant women was present in the serum of a few patients up to 24 days after the apparent elimination of malaria. Another explanation would be continued erythrophagocytosis by actively allergized macrophages. Severe haemolysis and gross splenomegaly are associated, as both have the same cause, but are not necessarily directly related, and persistent haemolysis can be observed without the spleen being palpable (Hamilton *et al.*, 1966).

Action of Steroids

The action of prednisolone and other glucocorticoid steroids on immunity is not clearly understood, but their administration is followed by lysis of lymphocytes and reduction of the mass of lymphoid tissue (Travis and Sayers, 1965). The effect of cortisone followed this pattern in rhesus monkeys (*Macaca mulatta*) infected by *P. cynomolgi* (Schmidt and Squires, 1951); the ascending infection was regulated by the innate immunity of the host and was not affected by the administration of cortisone; the infection precrisis, during crisis, and after crisis was controlled by the acquired immunity of the host and was profoundly affected by administration of cortisone. The phagocytic activity of existing macrophages was not

changed, but there was a great reduction of the usual proliferative lymphoid activity following infection, with more intense and prolonged parasitaemias. They interpreted these effects as due to lympholysis leading to the elimination of either a major source of new macrophages or of antibody production. Other workers have agreed that steroids have increased the severity of parasitaemia in various animals infected with different species of *Plasmodia* (Findlay and Howard, 1952 ; Redmond, 1952 ; Schneider, 1953 ; Jackson, 1955).

Accounts of the administration of steroids to humans with malaria are more difficult to assess, as always malarial supressives have been given at the same time. Schneider (1953) saw no effect on the course of a therapeutic infection with *P. vivax*, but Wurl *et al.* (1952) thought that the paroxysms of fever from *P. vivax* were blunted by cortisone ; there was some evidence that corticotrophin suppressed the haemolytic process without unduly worsening the parasitaemia in one patient with chronic *P. vivax* infection (Cook *et al.*, 1956). Demirağ and Sözer (1956) described the cases of two Turkish boys with recurrent malaria in whom haemolysis persisted with a positive direct Coombs reaction in spite of adequate antimalarial therapy ; cortisone in one and corticotrophin in the other arrested the haemolytic process. The administration of cortisone to patients with blackwater fever has been followed by dramatic improvement and cessation of haemolysis (Linley-Adams, 1953 ; Porte, 1954, 1955 ; Le Henand, 1956 ; Trowell and Vaizey, 1956). These experiences provide a parallel where one form of haemolysis, probably of an immune mechanism, involving malarial infection but not overt parasitaemia, was suppressed by corticosteroids.

There is no question that in five patients prednisolone stopped severe haemolysis which could not be controlled by other means. It probably had a beneficial effect in one other patient, but the P.C.V. rise was slow, possibly because of haemodilution and continued red cell sequestration associated with splenomegaly (Harrison, 1967): her Hb concentration rose to 11·3 g./100 ml. after at most five weeks' treatment with prednisolone, but this improvement cannot be attributed with certainty to steroid therapy.

The risks of steroid therapy must be balanced against the dangers of continuing severe anaemia and of repeated blood transfusions, especially hepatitis. It is the practice at Ibadan to consider steroid therapy only when there is severe anaemia (P.C.V. 18% or less) and haemolysis persisting after full malarial suppression, haematinic therapy, and three or four blood transfusions. The evidence for haemolysis is usually a falling P.C.V. and a raised reticulocyte count, but the possibility must be remembered that the reticulocytes may be raised as a result of haematinic therapy or haemorrhage, and a falling P.C.V. may be due to undetected haemorrhage.

There is a risk of unmasking infection by steroid therapy, and all patients were examined extensively and had a chest *x*-ray examination to exclude pulmonary tuberculosis. Treatment with steroids was usually started during the second trimester, and was continued into the puerperium, but it is probably better to reduce and finally stop treatment shortly before delivery ; this regimen would avoid depression of adrenal cortical activity and greater susceptibility to shock at delivery if haemorrhage occurs or an operative procedure is required. Also, resistance to genital tract infection in the puerperium would not be seriously impaired if steroids were stopped before delivery. There was the risk of patients defaulting and stopping treatment abruptly ; this happened in two patients, but apparently neither suffered any ill effect. Other Nigerians have been observed to stop steroid therapy without precipitating Addisonian crisis ; this is difficult to explain, as Africans have hydrocortisone production rates similar to those of Europeans (Thijssen *et al.*, 1967).

Steroid therapy did not appear to have any harmful effect on the fetus, and one death in utero was probably the result of severe maternal anaemia (P.C.V. 8%). This loss of one out of five infants in whom the outcome was known must be assessed against a background of a loss of about 40% in all pregnancies complicated by severe anaemia in Nigeria reported by Ojo (1965) and a loss of 17 (15%) out of 112 single pregnancies in the present series. A high incidence of perinatal mortality has been reported in women taking steroids during pregnancy ; Walsh and Clark (1967) lost 4 infants from 28 pregnancies and Warrell and Taylor (1968) lost 8 infants from 34 pregnancies and judged nine more fetuses to have been at a risk. These series are not strictly comparable, as the patients were receiving steroids throughout pregnancy, whereas the Nigerian patients did not start treatment until the second or third trimester.

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Deaths in Children with Acute Appendicitis

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Summary: Two hundred and four children died of acute appendicitis in England and Wales in the five-year period 1963–7. The mortality rate in children less than 5 years old was eight times higher than that in those aged 5–14. It is suggested that diagnosis, intravenous therapy, treatment of convulsions and hyperpyrexia, and anaesthesia are fields where there is room for improvement in management. Moreover, there is a place for the wider use of national medical audits on the lines of the Confidential Enquiry into Maternal Deaths.

Introduction

About 40 children die each year of acute appendicitis in England and Wales, representing about one death for every 780 hospital admissions with this diagnosis. It is tempting to feel that this number is virtually irreducible, but a previous limited survey by us suggested that in many children there are still avoidable factors contributing to death. We therefore decided to obtain information about all the children certified as dying of acute appendicitis in England and Wales during the five-year period 1963–7.

Method

We bought from the Registrar General a copy of the death certificates of children up to age 15 years whose death had been coded in I.C.D. Codes 550, 550·1, and 551. In these groups 229 deaths were coded, and we received this number of certificates. We extracted all certificates with a manifestly incorrect diagnosis, such as perforated caecum in neonates, and 18 which showed that the child had died at home. We then wrote to the records officer of the hospital concerned asking him to forward an enclosed letter to the consultant under whose care the child had been admitted. In this letter we set out the purpose of our investigation and asked for loan of the case notes or for some information about the patient. If we received no reply within two months we sent a second letter, and if there was still no reply we wrote to the local coroner if the death had been reported to him. In a number of instances we wrote a further letter to the hospital doctor asking for more details.

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Results

We wrote to hospitals regarding 200 children and eventually had a reply about 197. The sources of information on which the subsequent data are based are shown in Table I.

TABLE I.—*Source of Information*

Notes	128	Multiple	13
Letter	50	Certificates only	32
Coroner	6	Total	229

Incorrect Certification.—After we examined the 229 death certificates together with the replies to our inquiries we concluded that 25 were not "acute appendicitis deaths," which for the purpose of this survey we have defined as deaths resulting from acute appendicitis or an immediate complication of this disease, from a disease treated as acute appendicitis, or from a complication of the treatment of either of these groups. The correct diagnoses in these 25 patients are shown in Table II.

TABLE II.—*Diagnosis in 25 Cases Incorrectly Certified as Dying of Acute Appendicitis*

Perforated caecum	13
Complications of previous appendicectomy (e.g., adhesions)	8
Acute pancreatitis	1
Elective appendicectomy	3

"*Acute Appendicitis Deaths.*"—Two hundred and four children came into this category, and Table III shows the number dying in each of the years we studied.

TABLE III.—*Number of Children Dying of Acute Appendicitis in England and Wales, by Year of Death*

Year	1963	1964	1965	1966	1967	Total
No. of children	37	40	52	44	31	204

Figs. 1 and 2 and Table IV give information about admissions and deaths, and show the deaths per 1,000 for each sex, for two age groups, and for year of admission. The admission figures were obtained from the hospital inpatient inquiry (the data for 1967 are not yet available). Throughout the rest of this paper, when appropriate, we will give details for the age groups 0–4 years and 5–15 years. These results show very clearly the considerably higher death rate in the younger children. Though the under 5's make up only 7% of admissions they account for 37% of the deaths. The mortality rates