Summary and Conclusions

Thrombosis of the major pulmonary arteries is being increasingly recognized as a complicating event in a variety of illnesses.

The clinical and pathological findings are summarized in 19 further examples. In eight cases thrombosis was consequent on previous pulmonary embolism, in nine the findings suggested that autochthonous thrombosis had occurred. In two cases the pathogenesis was not established with certainty.

The pathogenesis and clinical effects are briefly discussed. Many of the patients have severe disease of the heart or lungs. The variability of the clinical effects attributable to pulmonary artery thrombosis is stressed. In this series they ranged from minimal changes to sudden intractable right heart failure.

Although the clinical changes are often masked by the underlying illness, the diagnosis may be suggested by a history of thrombophlebitis or embolism, by the occurrence of new and unexpected clinical signs and symptoms in the course of one of the predisposing illnesses, and on occasion by the radiological appearances.

Some patients show an illness characterized by recurrent embolization ; in others the presence of thrombotic obstruction is virtually symptomless until the onset of acute cor pulmonale. Less frequently, the thrombosis gives rise to a chronic cor pulmonale.

Thrombosis of the major pulmonary arteries may therefore have to be considered in the diagnosis of any case of acute, subacute, or chronic cor pulmonale.

I thank Dr. D. Dexter for his help and Professor T. Crawford for his assistance and advice in the preparation of the paper. Dr. D. Teare kindly allowed access to his material and records in Cases 16 and 18.

REFERENCES

Aitchison, J. D., and McKay, J. M. (1956). *Brit. J. Radiol.*, **29**, 398.
Ball, K. P., Goodwin, J. F., and Harrison, C. V. (1956). *Circulation*, **14**, 766.
Bedford, D. E., Papp, C., and Parkinson, J. (1941). *Brit. Heart J.*, **3**, 37.
Belt, T. H. (1939). *Lancet*, **2**, 730.
Brenner, O. (1935). *Arch. intern. Med.*, **56**, 1189.
Brill, I. C., and Robertson, T. D. (1937). Ibid., **60**, 1043.
Bryson, W. J. (1949). *Dis. Chest*, **15**, 366.
Campbell, M., Neill, C., and Suzman, S. (1957). *Brit. med. J.*, **1**, 1375.
Carroll, D. (1950). *Amer. J. Med.*, **9**, 175.
Covey, G. W. (1943). *Ann. intern. Med.*, **18**, 851.
Cugudda, E. (1952). *Minerva Med. (Torino)*, **43**, 205.
Cunningham, G. J. (1948). *J. Path. Bact.*, **60**, 379.
Gibbon, J. H., Hopkinson. M., and Churchill, E. D. (1932). *J. clin. Invest.*, **11**, 543.
Hanelin, J., and Eyler W. R. (1951). *Radiology*, **56**, 689.
Hodes, P. J., and Griffith, J. Q. (1941). *Amer. J. Roentgenol.*, **46**, 52.
Kampmeier, R. H. (1934). *J. thorac. Surg.*, **3**, 513.
Keating, D. R., Burkey, J. N., Hellerstein, H. K., and Feil, H. (1953). *Amer. J. Roentgenol.*, **69**, 208.
Magidson, O., and Jacobson, G. (1955). *Brit. Heart J.*, **17**, 207.
Means, J. H., and Mallory, T. B. (1931). *Ann. intern. Med.*, **5**, 417.
Middleton, W. S. (1943). Ibid., **18**, 343.
Rich, A. R. (1948). *Bull. Johns Hopk. Hosp.*, **82**, 389.
Ring, A., and Bakke, J. R. (1955). *Ann. intern. Med.*, **43**, 781.
Savacool, J. W., and Charr, R. (1941). *Amer. Rev. Tuberc.*, **44**, 42.
Trounce, J. R. (1953). *Guy's Hosp. Rep.*, **102**, 140.
Westermark, N. (1948). *Roentgen Studies of the Lungs and Heart*. Univ. of Minnesota Press, Minneapolis.
Whitaker, W., Heath, D., and Brown, J. W. (1955). *Brit. Heart J.*, **17**, 121.
Yater, W. M., and Hansmann, G. H. (1936). *Amer. J. med. Sci.*, **191**, 474.

"Extra Care Stops Falls" is the slogan adopted by the Royal Society for the Prevention of Accidents for this year's National Industrial Safety Week, which is to be held from September 29 to October 4. The theme forms the basis of a nationwide campaign directed to both managements and workers with the object of reducing the toll of industrial accidents, and particularly those associated with falls of persons. In 1956, 22,548 persons were absent from work as a result of injuries following falls, equal to 14.1% of all reported industrial accidents.

ANAEMIA OF UNCERTAIN ORIGIN IN INFANCY

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Severe anaemia in infancy and childhood is often seen at University College Hospital, Ibadan, Nigeria. In most cases anaemia occurs in association with conditions such as kwashiorkor, cancrum oris, tuberculosis, and chronic sepsis. Sickle-cell anaemia is also relatively common. However, many patients present, especially during the first two years of life, with severe anaemia unassociated with other recognizable diseases and not due to the sickle-cell gene. There has been much speculation about the aetiology and pathogenesis of anaemia in this latter group, and malignant tertian malaria and dietary deficiencies (chiefly protein and iron) have long been regarded as the most likely causal factors. Little has been done, however, to verify these speculations. We report here the results of investigation and treatment of 24 of these cases selected from 85 similar cases which occurred among 1,318 admissions to the children's ward during the period October, 1955, to June 30, 1956.

Case Selection.—In a busy ward with a very rapid turnover of cases, one cot was set aside and used exclusively for the investigation of children under 2 years of age with severe anaemia (haemoglobin, 5.9 g./100 ml. or lower). Sickle-cell anaemia and anaemia complicating some other illness were excluded. The 24 cases presented were those who were admitted into this cot.

Methods

Besides routine clinical examination the following were done: Tuberculin-testing by the Heaf technique was routinely performed and the majority of children had an *x*-ray examination of the chest and wrists. Haemoglobins were estimated, using Keeler M.R.C. grey wedge photometers (100% = 14.8 g./100 ml.). Thin blood films were stained with Leishman's and thick films with Field's stain. Supravital preparations, stained with brilliant cresyl blue (dried alcoholic solution), were made for reticulocyte determination (Whitby and Britton, 1953). Bone marrow was obtained by iliac crest puncture (Rubinstein, 1950), and smears were stained by Leishman and also by May-Grünwald–Giemsa. Differential marrow counts were made using the terminology of Dacie and White (1949) and red-cell maturation curves constructed (Pontoni, 1936). Serum protein estimation was performed by the biuret method, using a photoelectric colorimeter. Results were checked monthly against Kjeldahl. Liver-function tests consisted of thymol turbidity, zinc sulphate turbidity, alkaline phosphatase, and serum bilirubin, all performed with standard techniques. In four patients the serum cholesterol and in two the total serum lipids were estimated. Plasma volume estimation based on the single-injection technique of Chinard (1951) using Evans blue was performed on four patients before and after treatment. Sickling of the red cells was tested for by using a freshly prepared 2% solution of sodium metabisulphite. Cases showing sickling had samples of haemoglobin submitted for paper electrophoresis.

Routine Management

On admission, after blood and bone-marrow samples had been collected, each patient was given 200 mg. of "nivaquine" (150 mg. of chloroquine base) twice daily for three days. The only exception was Case 23, in which 25 mg. of mepacrine was given twice daily for three days. While in hospital all patients were fed by their mothers on food supplied only by them. We withheld comment on their feeding regimes. This course was decided on in order to eliminate alteration in the diet as a factor when assessing the results of treatment. Haemoglobin estimations and reticulocyte counts were done as often as possible. Blood transfusions were administered when it was considered that delay would jeopardize the patient's ultimate recovery. No haematinic was administered to any patient while in hospital, and indeed only one patient received ferrous sulphate, while attending the follow-up clinic. Complications were handled as circumstances warranted. After discharge patients were referred to a special follow-up clinic.

Results

Table I sets out the principal symptoms and signs, haemoglobins on admission, sickling, white-cell counts, and complications encountered.

History.—The average age of the patients was 9½ months (range 4 to 21); only two were over 12 months. There were 16 males and 8 females. The average duration of symptoms was 8½ days (range 1 to 60). All but three patients presented with fever; cough was present in 17 and vomiting in 10.

Diet.—With one exception (Case No. 1) all the patients were breast-fed. (Breast-feeding is almost universal in Ibadan during the first two years of life.) The majority in addition received a carbohydrate supplement in the form of "pap" (maize), "amala" (yam flour), and bread. Six mothers included a small ration of powdered milk in the dietary, and one of these also gave her child orange juice daily.

General Condition on Admission.—Despite severe anaemia 12 cases were in good condition and four fair. The contrast between haemoglobin level and apparent well-being was striking in many of these children. Fig. 1 shows Case 24 soon after admission when his haemoglobin was only 3.8 g./100 ml. It will be seen that he is bright-faced and apparently in robust health. On the other hand, Cases 1, 3, 5, 13, 15, 19, and 23 were very ill on admission and their general condition caused anxiety. There appeared to be no constant relation between haemoglobin level and the degree of illness manifested.

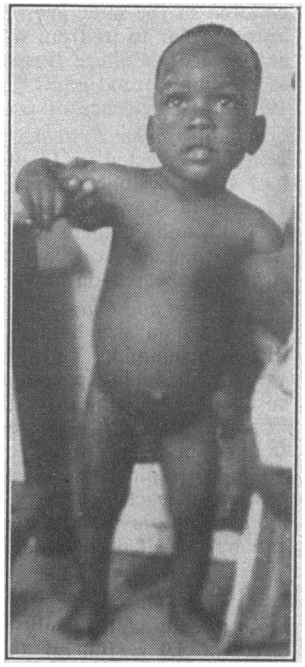

FIG. 1.—Case 24. The haemoglobin was 3.7 g./100 ml. when this photograph was taken.

Nutrition.—The majority were seen to be underweight, some grossly, when compared with standard weight curves for British and American children. The comparison is not valid because of vast social, economic, environmental, and genetic differences in the groups compared. Walters (1956), working in Ilobi, a typical Yoruba village in Western Nigeria, found that the average weight of normal children under 5 years of age was about 20% below that of English

TABLE I.—*Principal Symptoms and Signs, Haemoglobin, Sickling, White-cell Counts, and Complications in 24 Cases of Severe Anaemia in Infants*

Case No.	Age in Months	Sex	Symptoms: Fever	Cough	Vomiting	Diarrhoea	Duration in Days	Weight: lb. oz.	g.	Physical Findings: Gen. Cond.	Heart	Liver	Spleen	Blood: Hb g./100 ml.	Sickling	M.P.	W.B.C.	Complications
1	21	F	−	+	+	+	60	16 0	7,260	V. poor	S.M./E.	Palp.	2f	4·0	Nil	+		Respiratory infection + ascaris. Procaine penicillin
2	7	M	+	−	+	−	8	13 15	6,320	Good	S.M./T.R.	−	+	5·6	,,	+	9,800	Nil
3	9	M	+	+	−	−	5	14 14	6,750	V. poor	S.M.	3f	2f	5·1	,,	+		Respiratory infection. Procaine penicillin
4	7	F	+	−	−	−	2	12 9	5,695	,,	S.M.	3f	+	4·5	,,	+++		Persistent parasitaemia 3 days after nivaquine. Given mepacrine
5	8	M	+	+	−	−	10	15 8	7,030	Fair	N.A.D.	−	+	5·7	,,	+++	17,000	Respiratory infection. Sulphadimidine
6	9	M	+	+	+	−	8	9 2½	4,155	Good	N.A.D.	1f	+	4·9	,,	P.M.	18,200	Nil
7	12	M	+	+	+	+	6	17 7	7,910	Fair	S.M./E./T.R.	2f	+	3·8	,,	−		,,
8	9	F	+	+	+	−	5	12 13	5,810	Good	N.A.D.	1f	−	5·7	,,	−	10,900	,,
9	4	M	+	+	−	−	5	10 4	4,650	,,	N.A.D.	3f	4f	5·7	,,	−	13,600	Gastro-enteritis on 5th day. I.V. fluids + chlortetracycline
10	7	M	+	+	−	−	20	13 4	6,010	,,	N.A.D.	−	3f	5·5	,,	+	11,300	Nil
11	8	M	+	−	−	−	5	9 0	4,080	Poor	N.A.D.			5·5	Trait	−		Diarrhoea on 7th day. S.C. fluid + chlortetracycline
12	11	M	+	+	+	−	7	13 6	6,070	Good	N.A.D.	−	+	4·5	Nil	−	7,600	Nil
13	6	F	+	+	−	−	9	18 0	8,165	Moribund	S.M./E./T.R.	2f	−	4·7	Not done	−	24,300	*Died* soon after admission
14	11	M	+	+	+	+	6	14 8	6,575	Fair	N.A.D.	−	−	4·9	Nil	+G.	11,000	Nil
15	11	M	−	+	−	−	1	10 4	4,650	V. poor	S.M.	3f	4f	3·8	Not done	+		*Died* soon after admission
16	8	M	+	+	−	−	16			Fair	N.A.D.	1f	2f	4·9	Nil	+	10,400	Respiratory infection. Procaine penicillin
17	18	F	+	−	+	+	3	16 2	7,315	Good	N.A.D.	2f	2f	5·3	,,	+++	8,400	Nil
18	12	M	+	+	−	−	5	15 0	6,805	,,	S.M./E.	+	2f	5·9	,,	−	17,000	P.U.O. first 6 days then diarrhoea and dehydration. Sulphadimidine. S.C. fluid. S.C. saline
19	9	F	+	+	+	+	3	13 12	6,235	Dehydr.	N.A.D.	1f	2f	5·3	Trait	P.M. +G.		
20	5	F	+	+	−	−	2			Good	S.M./T.R.			4·8	Nil	+	8,200	Nil
21	8	M	−	+	+	+	5	15 0	6,805	,,	N.A.D.	−	+	5·1	Trait	−	50,200	,,
22	12	M	+	−	−	−	7	15 5	6,945	,,	S.M.	+	2f	5·1	,,	−	4,200	,,
23	6	F	+	−	−	−	7	13 13	6,265	V. poor	S.M.	2f	+	4·8	Nil	+		,,
24	12	M	+	−	−	−	3	22 0	9,980	Good	S.M.	+	1f	3·8	,,	−	16,000	,,

P.M. = pigmented monocytes. S.M. = systolic murmur. E. = enlargement. T.R. = triple rhythm. M.P. = malarial parasites. +G. = gametocytes present. 2f = enlarged 2 fingerbreadths.

children of the same age. Assessing our patients by standards familiar to us from work in the children's department at University College Hospital, Ibadan, most were classified as "within normal limits." Three patients (Cases 1, 6, and 19) showed evidence of mild protein malnutrition.

Cardiovascular System.—Nothing abnormal in the heart could be detected in 12 of our cases. The remainder all had apical systolic murmurs, and, in addition, Cases 1, 7, 13, and 18 showed enlargement of the heart, and in Cases 2, 7, 13, and 20 there was apical gallop rhythm. Case 13 was in congestive cardiac failure on admission. All cardiac signs disappeared on correction of the anaemia.

Abdomen and Chest.—The liver was palpable in 16 cases, and varied in size between 1 and 3 fingerbreadths below the costal margin. The spleen was enlarged in 19 patients, varying from "just palpable" to 4 fingerbreadths below the costal margin. The consistency of the organ was firm and in some patients it appeared to be tender. In spite of the frequent history of cough, only four patients showed evidence of mild respiratory infection. There were no positive tuberculin reactors. Cases 9, 11, and 18 were complicated by non-specific gastro-enteritis that developed in hospital, and were treated with parenteral fluids.

Haematological Findings

As already stated, only those patients with haemoglobin levels of 5.9 g./100 ml. (40%) or lower were included in the investigation. The blood-film appearances are summarized in Table II. It will be seen that in most films the cells were normochromic or slightly hypochromic, and that anisocytosis, poikilocytosis, and polychromasia were frequent findings.

Malarial parasitaemia was found in 13 cases, in all of which the parasite was *Plasmodium falciparum*. The initial reticulocyte count varied from 1% to 28% of total red cells, and in most the count was 5% or more. There appeared to be no relation between reticulocytosis and parasitaemia. The *bone marrow* showed a normoblastic hyper-

TABLE II.—*Red-cell Appearances in Peripheral Blood Film*

Case No.	M.P.	Hypochromic	Normochromic	Anisocytosis	Poikilocytosis	Polychromasia	Nuc. R.B.C. % Total Nuc. Cells	Retics. % Total R.B.C.
1	+	−	+	+	+	+	0	7
2	+	−	+	+	+	+	4	16
3	+	Slight	−	+	+	+	0	<1
4	+++	−	+	+	+	+	5	11
5	+++	+	−	+	+	+	0	20
6	P.M.	+	−	+	+	+	30	13
7	−	−	+	+	+	−	2	
8	−	+	−	+	+	+	0	9
9	−	+	−			+	6	10
10	+	−	+	+	+	+	0	16
11	−	+	−	+			0	<1
12	−	Slight	−				0	<1
13	−	+	−	+	+	+	2	2·5
14	+G	+	−	+	+	+	0	16
15	+	+	−	+	+		+	10
16	+	−	−	−	−	−	0	<1
17	+++	−	+	+	−	+	10	3
18	P.M.	Slight	−	+	+	−	0	10
19	+G	−	+	+	−	+	+	2
20	+	−	+	+	−	+	0	5
21	−	−	+	+	−	+	24	17
22	−	−	+	−	−	−	0	5
23	+	Slight	−	−	−	−	0	28
24	−	+	−				0	30

M.P.=malarial parasites. Nuc.=nucleated. +G=malarial gametocytes. P.M.+=pigmented monocytes.

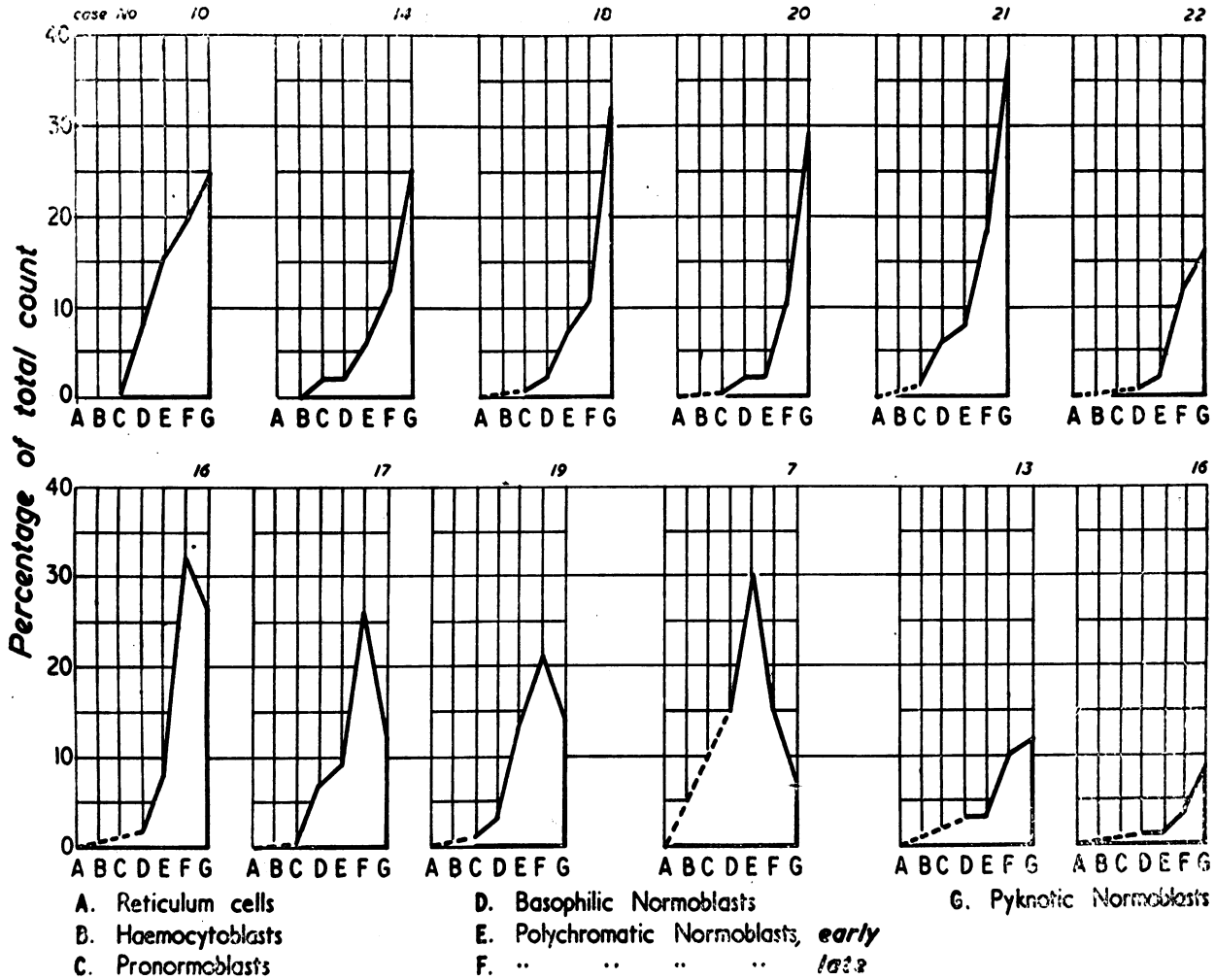

FIG. 2.—Anaemia of infancy presumed to be malarial. Bone-marrow red-cell maturation curves.

plasia in all but one of the patients from whom successful smears were made. Case 6 showed a mildly macronormoblastic marrow. There was evidence of very active erythropoiesis, with a greatly reduced leuco-erythrogenetic ratio (average 0.2:1; range 0.1–0.41:1) in all except Cases 13, 16, and 22, in which the ratio was within normal limits given by Dacie and White (1949)—namely, 0.56–2.67:1.

Bone-marrow maturation curves varied in pattern. Some cases showed a normal pattern with raised peaks, while others showed curves similar to those described for iron-deficiency and congenital haemolytic anaemias. Fig. 2 shows curves that were constructed for 12 cases in the series. Included for comparison are maturation curves after Dacie and White (1949) (Fig. 3).

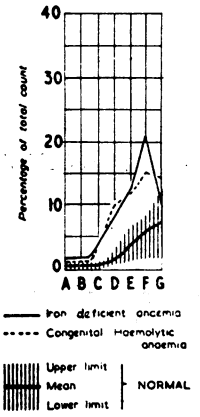

FIG. 3.—Maturation curves (Dacie and White, 1949).

Sickling tests were positive in Cases 11, 19, 21, and 22. Case 11 also had reduced osmotic fragility of the red cells. All four cases were, however, confirmed to be sickle-cell trait and not sickle-cell anaemia on paper electrophoresis of the haemoglobin.

The total *white-cell count* varied considerably, but in 9 of the 16 cases in which counts were done on admission the figure was below 12,000. Two of the remaining cases had counts over 20,000. The differential counts showed a polymorph preponderance in eight cases. Monocytes, many showing pigment granules, were conspicuous in the majority.

Plasma Volume Estimations.—We are indebted to Dr. H. Schneiden, of the department of physiology, for this investigation. Results of estimations done before and after a rise in haemoglobin level in four cases are given in Table III. It will be seen that in Cases 5 and 8 there was a fall in plasma volumes corresponding with a rise in haemoglobin. Case 6 showed no real change. Case 9 had the first test on the day before he contracted gastro-enteritis and became dehydrated. This may in part account for the rise in plasma volume in the second reading.

TABLE III

Case No.	Hb (g./100 ml.)	Plasma Vol.	Interval	Hb (g./100 ml.)	Plasma Vol.	Result
5	5·32	384 ml.	10 days	10·3	248 ml.	Fall 136 ml.
6	5·77	426 ,,	10 ,,	8·1	433 ,,	No change
8	5·1	542 ,,	9 ,,	7·4	324 ,,	Fall 218 ml.
9	5·77	242 ,,	9 ,,	9·64	298 ,,	Rise 56 ml.

TABLE IV.—*Serum Proteins, Liver-function Tests, and Serum Cholesterol in Infants with Severe Anaemia*

Case No.	Serum Proteins				Liver-function Tests			Cholesterol mg./100 ml.	Total Lipids mg./100 ml.	Alkaline Phosphatase K.A. Units
	Alb. g./100 ml.	Glob. g./100 ml.	Total g./100 ml.	A G Ratio	T.T. Units	$ZnSO_4$ Units	Bilirubin mg./100 ml.			
33	3·6	6·3	9·9	0·57	8		0·8	95	1,000	20·2
4	3·7	6·8	10·5	0·55				107	427	
5	3·0	3·3	6·3	0·91	6		0·8			7·7
6	3·3	2·8	6·1	1·18	3·5		1·9			9·15
7	3·2	3·5	6·7	0·9	9		0·52			23·9
8	2·8	3·3	6·1	0·85	9		0·54			24·0
9	2·8	1·8	4·6	1·5	6		0·51			11·4
10					5		1·0			19·8
12	3·5	3·0	6·5	1·17	4·5					15·3
13					4·0		1·0			17·4
14	3·4	3·1	6·5	1·1	4·5		0·4	55		19·4
16	3·0	2·7	5·7	1·1	9·5		0·4			13·0
17	3·35	3·25	6·7	1·0	12·0	18	0·8	135		
19	3·2	3·9	7·1	0·8	20·6	22·5	0·7			10·5
21					8·4	10·0	0·85			5·9
23*					7·5		0·2			34·5
24*					6·2	7·5	0·2			30·0

T.T. = thymol turbidity. $ZnSO_4$ = zinc sulphate turbidity.
* Liver function tests done after correction of the anaemia.
Comment: The high degree of systemic lipaemia in Cases 3 and 4 probably interfered with accurate globulin determination. In both these patients the serum presented an opaque, creamy appearance.

Serum Proteins.—The average serum albumin level in 12 cases was 3.24 g./100 ml. (range 2.8 to 3.7) and globulin 3.62 g./100 ml. (range 1.8 to 6.8), giving an A/G ratio of 0.89 to 1. Cases 3 and 4 showed abnormally high globulin levels which were thought to be false values occasioned by a high degree of systemic lipaemia which was present in these cases and interfered with accurate globulin determination. Excluding Cases 3 and 4, the average serum globulin becomes 3.07 g./100 ml. and the A/G ratio 1.05 (see Table IV). In order to provide a comparison, we examined the blood of some healthy non-anaemic children seen at an infant welfare clinic. Results are shown in Table V. The average serum albumin was 3.05 g./100 ml. (range 1.5 to 3.8) and average globulin 2.9 g./100 ml. (range 1.8 to 4.2), giving an A/G ratio of 1.05 to 1. Edozien (1957) records the average results of serum protein determinations on 200 healthy adult Nigerians as follows:

TABLE V.—*Results of Serum Protein Estimation, Liver-function Tests, and Serum Cholesterol Estimation in Healthy Infants at an Infant Welfare Clinic, University College Hospital, Ibadan*

Case	Age in Months	Serum Proteins				Liver-Function Tests			Cholesterol mg./100 ml.	Alk. Phos. K.A. Units
		Alb. g./100 ml.	Glob. g./100 ml.	Total g./100 ml.	A G. Ratio	T.T. Units	$ZnSO_4$ Units	Bilirubin mg./100 ml.		
WC/128	4	3·0	2·6	5·6	1·1	6·0	2·6	0·15	80	15·5
WC/191	10	3·2	2·0	5·2	1·6	4·9	4·0	0·5		32·6
WC/362	4	3·4	1·8	5·2	1·8	2·8	1·8			70·28
WC/28	15	3·0	3·1	6·1	0·96	6·5	2·8		124	75·9
WC/319	5	2·6	3·4	6·0	0·76	8·0	3·2	0·3		98·6
WC/324	3	1·5	4·2	5·7	0·35	2·2	2·4	0·15		14·2
WC/136	15					7·0	8·0	0·32	90	35·9
WC/380	1					0·6	4·5			
WC/378	1					0·6	4·2	0·4		
WC/318	9	3·4	2·8	6·2	1·2				70	
WC/—	2	3·6	3·0	6·6	1·12				118	
WC/—	12	3·8	3·2	7·0	1·18				128	

Comment.—The children selected for the above investigations were all well nourished and showed no clinical evidence of anaemia. Physical examination revealed no abnormality. Blood films of Cases WC/28, 319, and 324 were negative for malarial parasites. The remaining cases did not have blood films taken at the time the tests were performed. (The clinical assessment of these children was made by a senior paediatric consultant.)

Total protein	..	6.3±0.4 g./100 ml. (5.8 to 7.5)
Albumin ..	..	3.6±0.3 g./100 ml. (2.6 to 4.0)
Globulin ..	..	3.2±0.4 g./100 ml. (2.5 to 4.0)
A/G ratio	..	1.12 (0.8 to 1.5)

It will be seen that all the patients with anaemia and all but one of the welfare clinic cases (WC/324) had serum proteins within normal limits for Nigerians.

Liver-function Tests

Thymol turbidity tests performed on 16 patients gave high readings (Table IV). The average value was 7.7 units (range 3.5 to 20.6). The zinc sulphate turbidity test performed on four patients gave an average reading of 14.5 units (range 7.5 to 22.5). Similar tests performed on the welfare clinic cases gave the following results (Table V): thymol turbidity, average, 4.3 units (range 0.6 to 8); zinc sulphate turbidity, average, 3.7 units (range 1.8 to 8). It will be seen that, while there was close agreement in the results of serum protein estimation in the two groups compared, the results of the flocculation tests differ. The zinc sulphate turbidity depends almost entirely on the gamma-globulin fraction of the serum, and is a relatively accurate index of the concentration of the gamma-globulin (Kunkel, 1947, and Discombe *et al.*, 1954, quoted by Edozien, 1957). It would therefore appear that there was a qualitative difference in the globulin fraction in the two groups, caused by an increase in the gamma-globulin in the anaemic children.

Estimation of the *serum bilirubin* in 15 anaemic patients gave an average value of 0.7 mg./100 ml. (range 0.2 to 1.9). Only three patients had values above the accepted upper limit of normal. Results on six welfare clinic cases gave

an average of 0.3 mg./100 ml. (range 0.15 to 0.5). Serum alkaline phosphatase levels tended to be high in both the anaemic and the non-anaemic children seen in the welfare clinic. Three children in the latter group gave readings of 70.28, 75.9, and 98.6 K.A. units respectively. The explanation might be that these children had rickets, a not uncommon finding in Ibadan, but the possibility of a laboratory error cannot be overlooked. (These three tests were done on the same day).

Response to Treatment

There were two deaths in the series; both occurred within the first few hours after admission. Case 13 was desperately ill on admission and thought to be in cardiac failure. She was given 50 ml. of packed cells and appeared to stand the transfusion well. Three hours later she was given an intramuscular injection of 200 mg. of nivaquine, and died shortly after. Case 15 was admitted with a haemoglobin level of 3.7 g./100 ml. and was in very poor general condition but showed no evidence of cardiac failure. He was transfused slowly and given 80 mg. of nivaquine by intramuscular injection but died shortly after. In neither case were we able to obtain a necropsy, nor was the exact cause of death determined, but in both we suspected that the injection of nivaquine might have been causally related. They were, however, both very anaemic and very ill and the risks of transfusion in such cases are considerable. Despite the very large oral doses of nivaquine used in this series and in many other patients, we have not observed any toxic effects when the drug is given by this route, but we have been alarmed on several occasions at sudden collapse occurring within minutes of an injection of nivaquine in anaemic infants not otherwise ill.

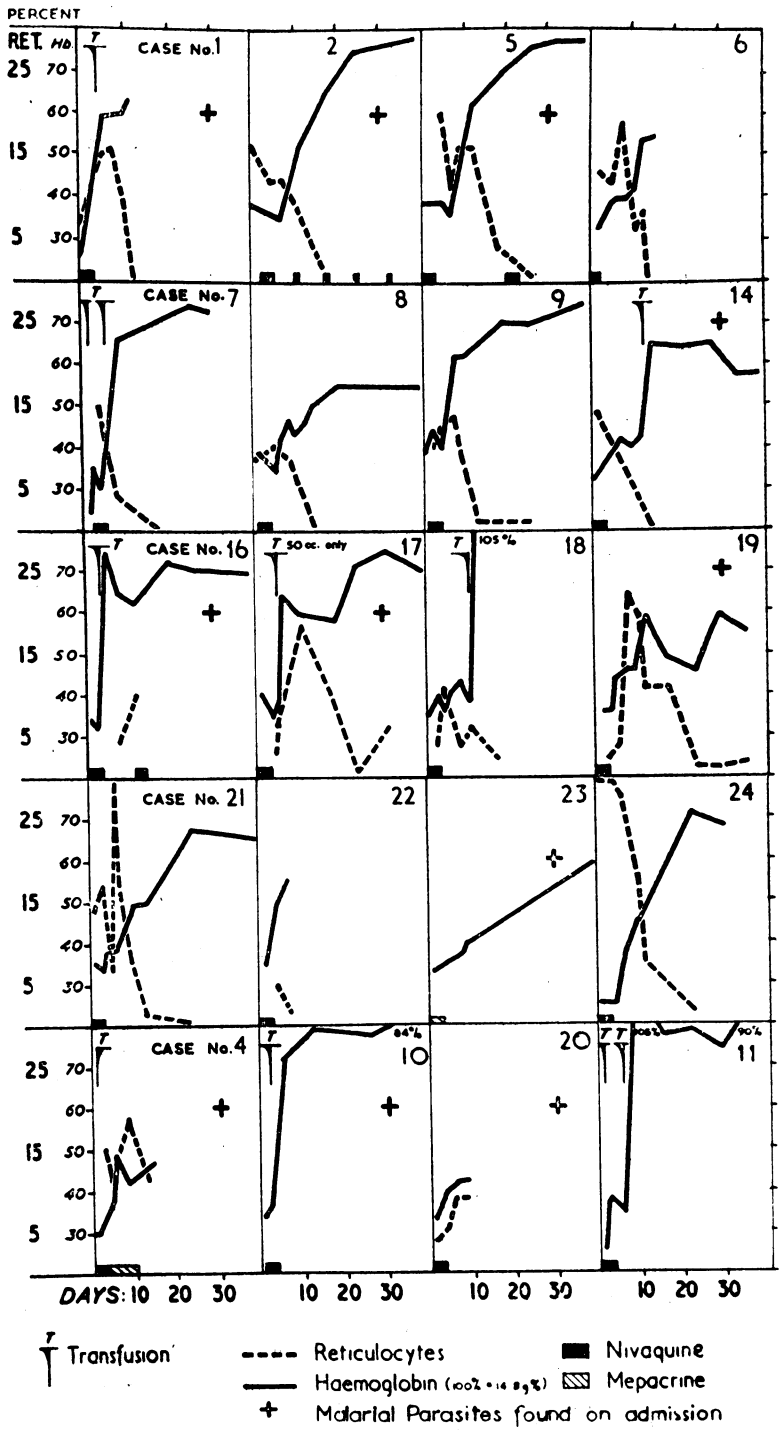

FIG. 4.—Anaemia of infancy presumed to be malarial. Haemoglobin and reticulocyte response to treatment.

Fig. 4 shows the response of haemoglobin and reticulocytes to treatment over 40 days in 20 cases. (Cases 3 and 12 are shown separately on Fig. 5.) It will be seen that in all the untransfused patients the haemoglobin rose steeply after a lag period of up to seven days. In some patients there was a slight initial fall in haemoglobin. In Cases 2, 5, 6, 9, 21, and 24 the rise in the haemoglobin was sustained at the rate of 0.3 to 0.4 g./100 ml. (2–3%) for 14 to 21 days, reaching levels of 10.36 g. (70%) after about 21 days. Cases 20 and 22 appear to have responded in a similar manner, but the records are short. Case 8 responded similarly, but the level did not rise above 8.14 g. (55%). The haemoglobin level in Case 19 pursued a more erratic course, rising to 8.6 g. (58%) by the 29th day and remaining at this level for six weeks, after which it rose to 10.66 g. (72%) without further treatment. Case 23 showed a slower but steady rate of increase of haemoglobin from 4.9 g. (33%) on the first day to 11.8 g. (80%) by the 75th day.

In most of the transfused patients the post-transfusion level of haemoglobin was maintained or it continued to rise. Cases 7, 10, and 17 show this well. Case 14 showed a fall from 9.6 g. (65%) after transfusion to 8.6 g. (58%) on the 40th day, but by the 56th day the haemoglobin had risen to 11.24 g. (76%).

Fig. 5 shows the result of a 200-day follow-up in Cases 3 and 12. Case 3 had frequent relapses (or reinfections) of malignant tertian malaria in spite of prolonged use of nivaquine and pyrimethamine (daraprim) orally. On two occasions after nivaquine had been given intramuscularly, blood films became negative, reticulocytes rose and then fell, and the haemoglobin rose. Possibly his mother had failed to give him his oral doses, but she seemed reliable, and attended regularly, and insisted that she had carried out our instructions. Notwithstanding the persistent parasitaemia and fluctuations in haemoglobin level, his weight showed a slow but steady rise except between the 60th and 70th days, when there was a fall associated with an attack of diarrhoea.

In Case 12 the haemoglobin level fell steadily after transfusion, when it was over

15 g., to 6.35 g. (43%) by the 102nd day. This fall was accompanied by return of malarial parasites in the peripheral blood film. Nivaquine was then given and the haemoglobin again rose to 12.72 g. (86%) by the 137th day. His weight showed a steady increase throughout. When parasites reappeared on the 150th day there was another fall in haemoglobin and weight. No treatment was given. The haemoglobin level became stationary at 10.95 g. (74%) and the weight at 18 lb. (8,165 g.), and both remained thus until the 218th day (not shown in Fig. 5). On the 250th day he had fever and was coughing, and the haemoglobin was found to be 8 g. (54%). Nivaquine was prescribed. On the 280th day, when he was last seen, his haemoglobin level was 10.36 g. (70%) and his weight 20 lb. 8 oz. (9,300 g.).

Reticulocyte response to nivaquine seemed to be of two types. The first, shown by Cases 1, 3, 4, 6, 9, 16, 17, 18, 19, 20, and 21, is typified by a peak about seven days after start of treatment, and conforms to Fairley's (1934) description of a reticulocyte crisis following administration of quinine in malaria. The second type, seen in Cases 2, 5, 7, 8, 14, and 23, consists of a high initial count falling steadily after the start of treatment.

Discussion

Ibadan is in a highly malarious area, and any investigation into the aetiology of anaemia, in any age group, occurring locally must perforce be influenced by this consideration. At the outset of the present investigation we could only guess at the contribution of malaria to the anaemia of infants. We aimed first to eliminate malaria as a variable by giving all our patients a large enough dose of nivaquine to be certain of controlling any latent or overt infection, and decided to use the drug irrespective of the presence or absence of parasitaemia. Besides malaria, the population of Ibadan, because of a deficiency of protein in their diet, suffer from protein malnutrition (Lawson and Lister, 1956).

Woodruff (1955), reporting on work carried out in Ibadan, states: "There is, therefore, evidence that anaemia in some African older children, adult males, and non-pregnant females may be associated with chronic protein malnutrition and liver damage, and this anaemia has the same characteristics as that found in young children and pregnant females." With this in mind, we paid particular attention to the dietary histories of our patients, and in order to avoid confusion we decided to keep them on their accustomed diets until the results of investigation showed the need for a change. The results set out above show that we were able to correct the anaemia in all our patients, without altering the diet, by giving them nivaquine, supplemented where necessary by blood transfusion. Of particular interest is the fact that improvement occurred irrespective of the initial presence or absence of malarial parasitaemia. Trowell (1949, 1956), working in Uganda, found

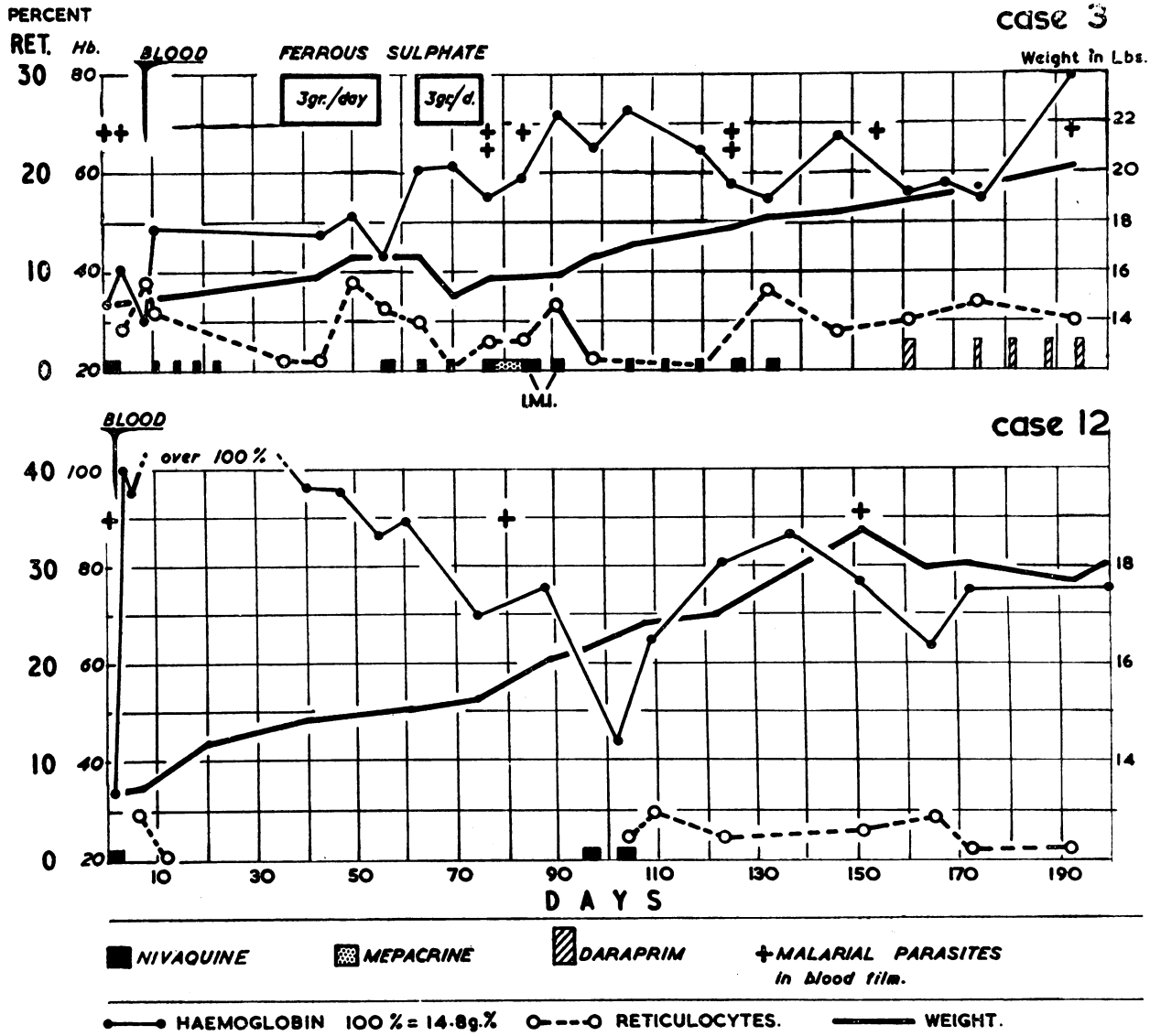

FIG. 5.—Anaemia of infancy presumed to be malarial. Haemoglobin, reticulocytes, and weight (200-day follow-up.)

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that in infancy severe anaemia is usually caused by malaria. He records that following quinine administration combined with a high-protein diet these infants show a reticulocyte response and rapid rise in haemoglobin level.

Iron deficiency is an important cause of anaemia in infancy. Milk-fed infants rely to a great extent on stores laid down in the liver in foetal life, and these in turn depend to some degree on the mother's diet during pregnancy. Premature infants are born with limited iron stores and are prone to hypochromic anaemia. Infections serve to increase iron requirements; infants reared in unhygienic surroundings are thus particularly subject to hypochromic anaemia (Holt and McIntosh, 1953). In Ibadan, maternal diets are generally poor, environmental conditions are unhygienic, and the incidence of prematurity is high (Lawson and Lister, 1956; Woodruff, 1951). It is surprising, therefore, that iron deficiency appeared to play no significant part in the pathogenesis of anaemia in our patients, who, without exception, recovered without being given iron. Clinical evidence and response to antimalarial treatment has led us to conclude that we were dealing with anaemia resulting from infection with *Pl. falciparum*. The efficacy of chloroquine in the treatment of malaria is well established (Trowell, 1956). However, the possibility exists that the drug might have acted in some other manner. Dähne (1943) found that quinine and mepacrine produced a reticulocyte response within three to eight days in normal non-anaemic and non-malarious subjects. He attributed this to a direct action on the bone marrow. In the absence of evidence to the contrary we must recognize the possibility that chloroquine might have acted in a similar manner in our patients.

Bruce-Chwatt (1952), working in Southern Nigeria, found the mean parasite rate in a sample of 138 infants to be: 0 to 3 months, 2.2%; 3 to 6 months, 60.0%; 6 to 9 months, 60–70%; over 9 months, ± 80%. It will be seen that prior to the third month of life the rate is negligible, but from then onward there is a sharp increase, so that by the age of 12 months 80% of infants have been infected. Reference to Table I will show that this "age of infection" corresponds in our patients with the age group in which anaemia is most common, but, whereas the parasite rate remains high after the first year, the incidence of anaemia declines. This decline in the incidence of anaemia is probably more apparent than real. After the first year the incidence of protein malnutrition rises and patients with anaemia and obvious malnutrition were excluded from the investigation. The explanation may, however, be bound up with immunological responses. During the first three months of life infants appear to be able to resist malarial infection. Thereafter susceptibility increases and anaemia might develop as part of the reaction of an individual with no acquired premunity to malaria. Survival of repeated attacks probably results in increased premunity, with consequent reduction in severity of clinical manifestations.

The anaemia of malaria is generally ascribed to haemolysis, though capillary haemorrhage may play a part (Strong, 1945). The essential features of a haemolytic anaemia are persistent anaemia, persistent reticulocytosis, hyperbilirubinaemia, and excess urobilinogen in the urine and in the faeces (Davidson, 1954). Our patients showed no evidence of haemorrhage. Jaundice was entirely lacking, and only three patients showed serum bilirubin levels slightly in excess of normal values.

In haemolytic anaemia the plasma bilirubin level usually lies between 1 and 3 mg./100 ml., but occasionally it is within normal range, normal levels being maintained by the ability of a healthy liver to excrete far more bilirubin than it is normally called upon to do (Dacie, 1954). Hepatomegaly and high values for the thymol turbidity and zinc sulphate turbidity tests in most of our cases suggest derangement of liver function. It seems unlikely, therefore, that normal serum bilirubin levels were maintained by healthy livers doing *more* than is usually required. In those patients in whom urine analyses were performed there was no excess urobilinogen. From our findings it seems improbable that haemolysis was the only factor in the pathogenesis of the anaemia. All our patients showed active erythropoiesis, and it is difficult to reconcile this with the anaemia, seeing that there was no convincing evidence of blood loss by haemorrhage or haemolysis. Woodruff (1951) found a similar discrepancy between the bone-marrow appearances and the peripheral blood in his cases of anaemia of pregnancy in Ibadan; and Altman and Murray (1948, quoted by Woodruff, 1951) made a similar observation in nutritional anaemia of infants.

One is reminded of thrombocytopenic purpura, in which, in spite of a hyperplastic marrow with an increase in megakaryocytes, there is a reduction in the number of platelets in the peripheral blood. Splenectomy often produces dramatic relief in these patients. Wiseman and Doan (1939) described primary splenic neutropenia in which there is agranulocytosis due to excessive phagocytosis of neutrophils in the spleen. The bone marrow in these cases shows a myeloid hyperplasia. Doan (1944, quoted by Nelson, 1945) suggests that "the spleen has an inherent capacity for unusual sequestration and destruction of the formed elements of the blood, and that this function may be stimulated to excessive activity by any condition which causes the spleen to enlarge. In such instances anaemia, leucopenia, and thrombopenia may result because the bone marrow in spite of hypertrophy is unable to compensate." It might be that disturbance of this function is operative in producing the peculiar blood picture which we have described. Results of plasma-volume estimation in our cases suggest that alteration in plasma volume may also be a factor in the pathogenesis of the anaemia.

Summary

Severe anaemia in infancy is often seen at University College Hospital, Ibadan. The results of investigation of 24 cases of severe anaemia in infancy are presented. The typical clinical picture was: a breast-fed baby about 9 months old presenting with fever, cough, and, in 50%, vomiting of one week's duration. Examination showed hepatosplenomegaly, and, in 50%, cardiac signs. The blood showed a normochromic or slightly hypochromic anaemia with anisocytosis, poikilocytosis, and polychromasia. The reticulocyte count was raised and the bone marrow showed a normoblastic hyperplasia. *Pl. falciparum* was found in 13 cases. Serum proteins fell within the normal range for adult Nigerians, and liver-function flocculation tests gave high values in most. The serum bilirubin was raised in only three cases. After correction of anaemia two cases showed a fall in plasma volume.

Treatment consisted only in giving nivaquine (chloroquine) in large doses irrespective of malarial parasitaemia, supplemented by blood transfusion when necessary. No haematinics were given, and patients were maintained on their accustomed diet. There were two deaths. The rest responded to treatment, untransfused patients showing a rapid rise in haemoglobin to normal. A reticulocyte response was noted.

Malaria is thought to be the cause of the anaemia. Malnutrition and iron deficiency play no significant part in the aetiology. The possibility that nivaquine might exert a specific haematinic influence is considered. The absence of evidence of gross haemolysis or haemorrhage in an anaemic patient showing active erythropoiesis is commented on, and it is suggested that abnormal splenic function ("hypersplenism") and alterations in plasma volume may be factors in the pathogenesis of the anaemia.

We thank Dr. A. B. Tompkins and Professor B. Elmes for permission to undertake this investigation; Dr. M. E. M. MacGregor for advice and encouragement; the house officers, ward sisters, and nursing staff of the children's ward for patient and willing co-operation; Mr. D. Simmonds for illustrations; and Mr. J. Garlick for electrophoretic studies.

REFERENCES

Bruce-Chwatt, L. J. (1952). *Ann. trop. Med. Parasit.*, **46**, 173.
Chinard, F. P. (1951). *Methods in Medical Research*, **4**, 38. Year Book Publishers, Chicago.
Dacie, J. V. (1954). *The Haemolytic Anaemias.* Churchill, London.
—— and White, J. C. (1949). *J. clin. Path.*, **2**, 1.
Dähne, G. (1943). *Dtsch. tropenmed. Z.*, **47**, 129. Abstracted by B. G. Maegraith, *Trop. Dis. Bull.*, 1950, **47**, 202.
Davidson, L. S. P. (1954). *The Principles and Practice of Medicine*, 2nd ed. Livingstone, Edinburgh and London.
Edozien, J. C. (1957). *J. clin. Path.*, **10**, 276.
Fairley, H. (1934). *Brit. med. J.*, **1**, 451.
Holt, L. E., and McIntosh, R. (1953). *Holt Pediatrics*, 12th ed. Appleton-Century-Crofts, New York.
Lawson, J. B., and Lister, U. G. (1956). *Clinical Report of the Department of Obstetrics, University College Hospital, Ibadan.* Vail, London.
Nelson, W. E. (1945). Mitchell-Nelson *Textbook of Pediatrics*, 4th ed. Saunders, Philadelphia and London.
Pontoni, L. (1936). *Haematologica*, **17**, 833.
Rubinstein, M. A. (1950). *Ann. intern. Med.*, **32**, 1095.
Strong, R. P. (1945). In *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, 7th ed., vol. 1. Lewis, London.
Trowell, H. C. (1949). *Trans. roy. Soc. trop. Med. Hyg.*, **42**, 417.
—— (1956). *Trop. Dis. Bull.*, **53**, 121.
Walters, J. (1956). "The Health of a Yoruba Village in Western Nigeria." From an address delivered to the Clinical Society, University College Hospital, Ibadan. To be published.
Whitby, L. E. H., and Britton, C. J. C. (1953). *Disorders of the Blood*, 7th ed. Churchill, London.
Wiseman, B. K., and Doan, C. A. (1939). *J. clin. Invest.*, **18**, 473.
Woodruff, A. W. (1951). *Brit. med. J.*, **2**, 1415.
—— (1955). Ibid., **1**, 1297.

PROLONGED ANURIA COMPLICATED BY EPILEPTIFORM FITS

BY

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The dietary and fluid restrictions imposed on patients with anuria has been fully described (Bull *et al.*, 1949; Merrill, 1955). The occurrence of severe convulsions late in the course of treatment is not a generally recognized complication.

The patient whose case is described below had very severe epileptiform fits on her 17th day of anuria, and recovered. The management and aetiology of the fits, as well as the nature of the residual renal lesion and its effect on child-bearing, are discussed.

Case History

A primigravida aged 26 was first seen on March 25, 1955, at the 25th week of pregnancy. Her blood pressure was 130/80 mm. Hg; there was no proteinuria or past history of renal disease. During the 29th week of gestation she was admitted to hospital complaining of abdominal pain, vomiting, absence of foetal movement, and anuria for some hours. She was pale and anxious, and her blood pressure was 140/90. There had been no vaginal bleeding. A small quantity of urine was obtained from the bladder by catheter, and there was no proteinuria.

On examination the uterus was hard and tender, and foetal parts could not be palpated nor the foetal heart heard.

Two pints (1,100 ml.) of blood was given, and three hours after admission uterine contractions were felt, so the forewaters were ruptured. Eight hours later a stillborn foetus was expelled, with 5 pints (2,840 ml.) of blood clot and the placenta. A further 2 pints (1,100 ml.) of blood was transfused. No fall in blood pressure had occurred since she was admitted to hospital.

After delivery no further obstetrical complication arose, but complete anuria persisted for the first 11 days, and oliguria for another six (see Table and Chart). The anuria

Fluid Intake and Output

Day	Input (ml.)				Output (ml.)		
	Mouth	Intra-gastric Drip	Intravenous Drip	Total	Urine	Vomit	Total
1	780	—	1,000 (blood)	1,780	—	—	—
2	120	600	1,000 (blood)	1,720	1	—	1
3	—	1,000	—	1,000	28	—	578*
4	—	800	—	800	—	—	—
5	800	—	—	800	10	150	160
6	800	—	1,000 (blood)	1,800	—	—	—
7	800	—	—	800	—	30	—
8	840	—	—	840	100	803	903
9	—	800	—	800	—	510	510
10	—	500		500	—	350	350
11	—	400	500 (blood)	900	—	240	240
12	—	500	—	500	510	360	870
13	495	—	700	1,195	150	105	255
14	480	—	1,000	1,480	270	—	270
15	180	—	1,025	1,605†	330	—	330
16	—	—	1,000	1,600‡	360	30	390
17	—	—	1,940	1,940	690	—	690
18	—	—	1,600	1,600	1,080	—	1,080
19	—	—	2,300	2,300	1,875	135	2,010
20	—	—	3,000	3,000	2,130	150	2,280
21	—	—	3,000	3,000	2,475	30	2,505
22	—	—	3,500	3,500	3,540	255	3,795
23	30	—	4,500	4,530	3,600	30	3,630
24	210	—	4,500	4,710	4,860	150	5,010
25	600	—	6,000	6,600	5,100	30	5,130
26	450		6,000	6,450	6,960	—	6,960
27	1,040	—	5,000	6,040	5,490	90	5,580
28	2,500	—	4,000	6,500	6,120	—	6,120
29	2,625	—	4,000	6,625	6,480	—	6,480
30	4,130	—	2,500	6,630	5,295	—	5,295
31	4,230	—	900	5,130	4,065	—	4,065

* 550 ml. in faeces. † 400 ml. by enema. ‡ 600 ml. by enema.

was treated on conventional lines at first, with 400 g. of glucose, 100 g. of peanut oil, emulsified to 1 litre of water (Bull *et al.*, 1949). As the anuria persisted the quantity of fluid was reduced to 800 ml. a day, given by mouth as 50% glucose with adequate vitamins. Excessive vomiting occurred on the eighth day, and the fluid was then given by intragastric drip: further attacks of vomiting necessitated changing to 40% glucose, given by caval drip (de Keyser *et al.*, 1949; Bull, 1952; Russell *et al.*, 1954). The electrolyte balance of the patient was followed at frequent intervals, and on the 12th day the serum potassium had risen to 7.6 mEq/l. This was reduced to 4.2 mEq/l. by giving 100 g. of "zeo-carb. 225/Na," suspended in 1 litre of water, administered in five divided doses over two days. The anaemia was twice treated by transfusion of concentrated red blood cells, 2 pints (1,100 ml.) on the sixth day and 1 pint (550 ml.) on the eleventh day.

Epileptiform Fits.—On the 17th day, just as renal function was returning, a series of epileptiform fits occurred, and at the first fit a blood pressure of 220/90 was recorded (a blood pressure of 170/100 had been recorded earlier in the day, a slight rise over the 160/80 of the day before) (see Chart). These fits were not controlled by the prompt administration of 4½ gr. (0.3 g.) of phenobarbitone sodium intramuscularly, nor by 3 g. of NaCl intravenously. The fits started to come at ever-increasing frequency and violence, 10 occurring in about two and a half hours. Thiopentone sodium, 0.5 g. intravenously, brought immediate respite, and a further 0.25 g. was given when muscular twitching became apparent 15 minutes later. Bromethol ("avertin"), 6 ml. in 8 oz. (230 ml.) of water, was given, and this was followed by a fall in the blood pressure to 140/90. A further 4 ml. of bromethol was given three hours later, when the blood pressure had risen to 195/110. The blood pressure then fell to 165/90, and did not rise again, nor did fits recur. Sodium amylobarbitone, 3 gr. (0.2 g.), was given intravenously for the next six nights, which kept her in a very drowsy state. She was discharged from hospital on the 43rd day after the onset of the concealed accidental haemorrhage.