TREATMENT OF THE CHRONIC ALIMENTARY ENTERIC CARRIER*

BY

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The problem of the enteric carrier has exercised many penetrating minds and has evoked a large amount of work, thought, discussion, and compassion, and a sizable literature over the last half-century. Many conflicting views have been put forward in recent years regarding the efficacy of treatment. In Scotland, where standards of health and hygiene are high, the relatively small nidi of enteric carriers probably represent the last stronghold of a disease which in former years has taken its toll of human life and suffering. In the world at large, however, and particularly in the relatively underdeveloped countries, the problem must still be a vast one. The carrier's condition is a danger not only to the community but to himself in the form of restriction, anxiety, and painful and even potentially fatal disease.

Present Investigation

My attention was first drawn to the carrier problem in the course of surgical practice in Bellsdyke Hospital, Larbert, in 1954, by Dr. Alan P. Russell. There was a nidus of nine alimentary enteric carriers—eight faecal excretors of *Salmonella paratyphi B* and one mixed alimentary carrier excreting intermittently *Salm. typhi* and *Salm. paratyphi B*. Eight of them had been discovered during an intensive investigation in 1951, and in May, 1956, a ninth carrier was transferred from another hospital. These carriers were kept in isolation and therefore were excluded from communal social intercourse, group therapy, and rehabilitation. Their restriction was responsible for considerable anxiety and frustration, and prevented advancement in their status within the hospital community. In addition to this, they formed a pocket of potential disease, not only within the hospital but also outside its walls. Indeed, one of the nursing assistants developed overt enteric fever while on leave in Ireland.

In 1954 the question of surgical treatment for the carrier group was discussed, but a study of the recent literature and some of the standard works left one with mixed feelings about the possible benefits of surgery, and no action was taken. In 1956, however, one of the patients developed an acute illness which necessitated surgical treatment as a matter of urgency.

Treatment of Case 1

The patient had an episode of cholecystitis in October, 1956, and in the following January again complained of abdominal pain and developed jaundice, which gradually deepened. Murphy's sign was positive, but the gall-bladder was not palpable. Bile was present in the urine. A plain x-ray film showed no evidence of stone. Liver-function tests indicated that the jaundice was of obstructive type, and, as it was persistent, laparotomy was undertaken on February 22, 1957.

The gall-bladder and bile-duct system were found to be distended, fibrotic, subacutely inflamed, and buried

in dense adhesions. When the adhesions were being freed it was noted that the duodenum was firmly fixed to the gall-bladder wall. In separating the necrotic duodenum a perforation occurred. This was sutured in two layers. Cholecystectomy and choledochostomy were performed with considerable difficulty. Convalescence was rather stormy.

After operation this patient showed positive stools for four months. Thereafter the stools became persistently negative and have remained so up to the present. It is significant that his post-operative environment was not changed and that he continued to live in the isolation ward with the eight other carriers who continued to excrete the organisms. Even by the most rigid standards, therefore, his carrier state must be considered to have been eliminated.

Treatment of Cases 2-9

In view of the successful outcome of this case it was decided to carry out cholecystectomy, if possible, in all the remaining carriers, and arrangements were made for radiological, biochemical, and histological studies.

During the treatment and studies stringent aseptic precautions were enforced and the staff involved were immunized. No case of enteric fever or P.U.O. has occurred. As the patients were regarded as a "carrier unit" an antiseptic attack was carried out on their clothing, utensils, and accommodation on completion of treatment.

In June and July, 1958, the remaining eight carriers were submitted to cholecystectomy. The detailed findings are discussed later. No patient died and there was no significant morbidity. On the contrary, it has been generally agreed that the general state of health of the patients is much improved.

Courses of oral neomycin were given to all of the carriers in September and December, 1957, and again in September, 1958.

Results of Treatment

When a new carrier was added to the group the total monthly numbers of positive stools rose (see Chart). The first course of neomycin seemed to cause some diminution in faecal excretion, but it was only after all carriers had had cholecystectomy that faecal excretion was abolished.

Monthly total of positive stool cultures in the carrier group.

There seems reason to believe that a post-operative course of neomycin may shorten the period of post-operative persistence of excretion. Since only 3% of the oral dose is believed to be absorbed, the drug probably has its action locally in the bowel, where it kills those organisms excreted with the bile. Case 2 showed a positive stool culture in February, 1959 (see Chart). This patient was the only one who appeared to relapse;

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his further progress and treatment are discussed later. Post-operative stool cultures were actually made at fortnightly intervals.

The records showed that none of the patients could be classified as a urinary carrier.

Survey of the Literature

As much of the available literature as possible was obtained. A total of 83 works—most of them in English—were consulted and analysed.

Anton and Fütterer (1888) were apparently the first to show that *Salm. typhi* could be isolated from the gall-bladder in fatal cases of the disease, and Blachstein (1891) recorded that *Salm. typhi* injected intravenously into rabbits soon established itself in the gall-bladder. Findlay and Buchanan (1906) isolated organisms from the gall-bladder 25 years after an attack of typhoid fever and at the same time demonstrated them in the faeces. In some cases—for example, Dudgeon (1908)—*Salm. typhi* had been isolated from the gall-bladder in cholelithiasis where there was no history of typhoid fever. Robert Koch in 1902 had drawn attention to the typhoid patient or convalescent as the most serious source of spread of the disease.

Dehler (1907) reported the treatment of two carriers by cholecystostomy, and Grimme (1908) described the cure of a patient by cholecystectomy. Thereafter reports of single cases and series operated upon occur in the literature. The procedures recommended were cholecystectomy, cholecystostomy, and cholecystectomy with drainage of the common bile-duct. It is interesting to note that pioneering work in this field was carried out in the wards of the Western Infirmary, Glasgow, in 1923-4. Cholecyst-gastrostomy was carried out on two carriers by Mr. Farquhar Macrae, after observing that typhoid and paratyphoid organisms were rapidly killed in human gastric juice. One patient (a typhoid carrier) was pronounced cured, but the other (a mixed carrier) was not, and was subsequently submitted to cholecystectomy with drainage of the common bile-duct. For 14 months the stools were positive on several occasions, but later were negative for three years. A third (paratyphoid) carrier was cured after cholecystectomy and duct drainage.

TABLE I.—Results of Surgical Treatment of Carriers

Author	No. of Cholecystectomies	Mortality (if Stated)	Cured		Remarks
			No.	%	
Browning <i>et al.</i> (1933)	57		43	75	Review
Senftner and Coughlin (1933)	68	14.7%		68	"
Hanssen (1935, quoting Berglas)				75	
Hanssen (1935)	5	Nil		100	
R.M.P.A. (1936)		21%		77	"
Lobsenz (1936)	1	Nil			
Coller and Forsbeck (1937)	18	"		100	Quota-tion
Lynn (1937)				80-85	
Levi and Willen (1941)	1	"			
Vogelsang (1941)	13		8		
Badia (1941)	1	1			
Coller and Crabtree (1942)	18		16	88.9	
Honig (1943)	1	Nil			
Feemster and Smith (1945)	68		63	88.9	Review
Stout <i>et al.</i> (1947)	1	"	1		
Littman <i>et al.</i> (1949)	13		12	92.3	
Vogelsang (1950, quoted by Flynn, 1957)				80	
Pearson and Wolfe (1950)	1	"	1		
Lemmon <i>et al.</i> (1957)	4		4	100	
Flynn (1957)	6	1	5	83.3	

The average rate of cure was 85%.

Browning *et al.* (1933) made a comprehensive review of the whole subject of chronic enteric carriers and their treatment.

Surgical Treatment.—Table I presents an analysis of the results of surgical treatment of the carrier state, as extracted from the later literature. While the adequacy of the criteria as regards pre-operative duration of carrier state and period of post-operative observation cannot be regarded as acceptable in all cases, the cure rate from surgical treatment appears to be in the region of 85%.

Medical Treatment.—Early medical measures, which covered a wide field of therapeutic methods, were uniformly unsuccessful. With the introduction of specific therapy in the form of sulphonamide drugs and antibiotics a new era of hope dawned, and it was believed that a drug would soon be found which would eliminate the carrier state. Table II, extracted from the literature,

TABLE II.—Results of Medical Treatment of Carriers

Therapeutic Agent	No. Treated	No. Cured	No. Treated	No. Cured
Sulphaguanidine	30	3	44	3
Succinylsulphathiazole ..	7	0		
Sulphadiazine	7	0		
Penicillin + sulphamerazine	5	3	41	11
" + sulphathiazole	36	8		
"	1	1	34	3
Streptomycin	8	2		
Chlortetracycline	2	0		
Oxytetracycline	2	0		
Chloramphenicol	21	0		
Total	119	17		

The average rate of cure was 14%.

shows that of 119 carriers so treated only 17 (14.3%) have been cured. The high hopes held out for modern medical treatment have therefore not yet been realized.

Analysis of Results of Investigations

Excretion Frequency in the Carrier State.—The "excretion frequency" of the carrier state from January, 1956, to the time of cholecystectomy in each of the nine carriers was estimated from the relative numbers of positive and negative stool cultures. The number of positive cultures is expressed as a percentage, and when this figure is allotted to each carrier they can be arranged in descending order of excretion frequency. It seemed pertinent to ascertain whether the severity of the infection in the different carriers, as evidenced by their excretion frequency, bore a significant relationship to the following features, which were recorded for each carrier: (1) pre-operative serum bilirubin; (2) radiological evidence of pathological changes in the gall-bladder and bile ducts; (3) evidence at operation of pathological changes in the gall-bladder and bile ducts; (4) culture of common-duct bile; and (5) microscopical features of the excised gall-bladder.

Pre-operative Excretion Frequency Related to Serum Bilirubin.—There is a tendency to a higher serum bilirubin level in the more persistent carriers (Table III).

Pre-operative Excretion Frequency Related to Radiological Findings.—The radiological findings have been separated into four grades, corresponding to function on oral and intravenous cholecystography. The grades of function are seen to follow closely the excretion frequency (Table III). (Case 8 is the only exception, and it is doubtful whether this patient ingested the oral dye.) The radiological reports, as in the case of all other findings, were made without knowledge of the excretion frequency.

Pre-operative Excretion Frequency Related to Operative Findings.—The excretion frequency was found to be directly related to the naked-eye evidence of disease of the extrahepatic biliary system. (Details have been omitted because of lack of space.)

Pre-operative Excretion Frequency Related to Gallstones and to Positive Cultures of Common-duct Bile.—Apart from Case 1, in which there was a highly acute cholecystitis, the most persistently positive carriers had one or more stones in the gall-bladder (Table III). Bile cultures from the common duct were positive in the four most persistently positive carriers. It is concluded that living enteric organisms are found in the common bile duct in the carrier state. They can be constantly cultured from this site in the most persistent carriers.

Pre-operative Excretion Frequency Related to Histological Findings in the Excised Gall-bladder.—The excretion frequency (Table III) has been found to be directly related to the degree of inflammatory change in the gall-bladder wall, the constant faecal excretors showing evidence of subacute or acute-on-chronic inflammation, the intermediate excretors showing evidence of mild chronic cholecystitis, and the occasional excretors showing virtually no evidence of the inflammatory process. The changes, which consist of infiltration with plasma cells, lymphocytes, and (in the more constant excretors) polymorphs, often in well-marked "follicle" formation, are of greatest intensity in the submucosa and fade as the deeper layers and serous surface are approached, suggesting that the gall-bladder is infected via the bile and not via the blood-stream. There is no evidence, in the present series, that the intensity of the changes is related to the duration of the carrier state. It seems very doubtful whether any antibiotic could justly be expected to eradicate this type of infection even if it could reach the diseased gall-bladder in sufficient concentration.

Prospect of Spontaneous Cure.—A survey of the monthly records of faecal cultures over the five-year period 1952–6 for the eight carriers shows no evidence whatever of a tendency to spontaneous cure.

Post-operative Observations

In addition to fortnightly stool cultures various other observations were made at monthly intervals.

Liver-function Tests.—During the four months after operation no significant abnormality was observed in thymol turbidity or serum alkaline phosphatase estima-

tions, but in Case 2 the serum bilirubin level was found to be abnormally high and to fluctuate. Since the thymol turbidity and serum alkaline phosphatase levels did not rise, continued ductal infection was suspected in this patient in spite of negative stool cultures.

Blood Sedimentation Rates.—In seven of the carriers these rates remained within normal limits over a four-months' post-operative period, but in Cases 2 and 3 there was a persistent and significant elevation. In Case 3, however, a degree of anaemia was found, and when correction was made for this the elevation was not considered significant.

Widal Tests.—A study of monthly post-operative Widal tests yielded the following information: (a) the phenomenon of coagglutination noted by Browning *et al.* (1933) was again seen; (b) it was found that a positive "H" titre tended to remain after cholecystectomy; and (c) in only one patient (Case 2) was a positive "O" titre found post-operatively, and it was persistent.

Further Progress of Case 2

Although this patient's stool culture was negative after operation, his progress was watched with some concern for the following reasons: (1) he was one of the two most constant faecal excretors; (2) at the original operation the common bile duct had been considerably dilated and had been drained by T-tube; (3) of the nine carriers, his serum bilirubin alone was fluctuating and rising; (4) of the nine, his E.S.R. alone was significantly elevated; and (5) of the nine, he alone retained a positive *Salm. paratyphi B*, "O" titre.

In February, 1959, this patient developed overt relapse and a positive stool culture was obtained. Isolation and barrier nursing were instituted.

On February 8, 1959, intravenous cholangiography was performed to determine whether there was evidence of common-duct scarring, stone, or stasis. The outline of the duct was found to be normal and there was no evidence of stone. At 100 minutes after the injection, however, no dye had entered the duodenum and there was considerable dilatation.

On February 12 a further operation was undertaken. The common bile duct was re-exposed and found to be thickened and distorted. Choledochotomy was performed and the lining was found to be rather vascular and inflamed. No stones were present in the duct or in the right and left hepatic ducts. A fine bougie passed

TABLE III.—Summary of Results of Investigations

Case No.	Excretion Frequency %	Serum Bilirubin (mg./100 ml.)	Graded Radiological Findings	Stones	Bile Culture	Histology of Excised Gall-bladder
1	84	10.5	Jaundice	—	+	Focal ulceration of mucosa. Dense infiltration of mucosa with chronic inflammatory cells. Areas of polymorph infiltration. Extension of inflammatory infiltrate between the muscle layers. <i>Subacute ulcerative cholecystitis</i>
2	83	0.8	4	+	+	Degenerative change in mucosa which is atrophic. Remnants of mucosa densely infiltrated by chronic inflammatory cells, the infiltration extending fairly deeply to muscularis. Subserous and submucous fibrosis. <i>Chronic cholecystitis</i>
3	53	1.0	3	+	+	Marked diffuse chronic inflammatory infiltrate, especially in the mucous membrane. Some oedema between muscle bundles. <i>Chronic cholecystitis</i>
4	33	0.8	2	+	+	Mucosa atrophic. Muscularis replaced by connective tissue. Foci of inflammatory infiltrate in mucosa, indicative of continued infection. <i>Low-grade chronic cholecystitis</i>
5	23	0.8	2	—	—	Gall-bladder wall very vascular. Sprinkling of chronic inflammatory cells in mucosa, spreading deeply via crypts. One aggregate of inflammatory cells. <i>Mildly chronically inflamed gall-bladder</i>
6	14	1.0	1	—	—	Slight fibrosis of submucous, muscular, and subserous coats. No sign of active inflammation
7	10	0.2	1	—	—	Mucosa thin and a little simplified. Partial fibrosis of muscularis. <i>Some evidence of past inflammation. No sign of activity</i>
8	10	0.2	23	—	—	General architecture normal. Gall-bladder thin-walled. Muscle probably congenitally poor. <i>No sign of infection, past or present</i>
9	8	0.2	1	—	—	Mucosal pattern complex. The wall showed <i>no sign of infection, past or present</i>

into the duodenum after some initial resistance. The anterior wall of the duodenum was therefore incised and choledochal sphincterotomy performed under direct vision. The common duct was drained by a T-tube and the duodenal defect sutured in the transverse diameter. The wound was closed with drainage. The appendix was removed.

No enteric organisms were cultured from bile or appendix, and on histological examination the latter organ showed evidence of only mild previous inflammation.

While the T-tube was in position a solution containing 0.5 g. of neomycin was injected along it twice daily for two weeks and the tube was removed on March 25. Cholangiography, performed before removal, showed free passage of the dye into the duodenum.

Convalescence after this secondary operation was quite uneventful and stool cultures have remained negative until the time of writing. The serum bilirubin has reverted to a fairly constant figure of 1 to 1.5 mg./100 ml., the E.S.R. is receding, and the "O" titre has disappeared from the serum.

Present Position of the Nine Carriers

One carrier has had consecutively negative stools for 37 months since operation (74 examinations); six have had consecutively negative stools for 24 months since operation (48 examinations); one has had consecutively negative stools for 22 months since operation (44 examinations) and one has had consecutively negative stools for 17 months since the secondary operation (34 examinations).

Discussion and General Conclusions

It is now more than half a century since it was first realized that chronic carriers played a part in the dissemination of enteric fever. A study of the role of the gall-bladder and biliary tract over the years has led to the gradual realization of its importance in relation to biliary carriers. It is contended that the present studies establish beyond reasonable doubt its culpability in the alimentary carrier. The carriers have been graded according to their "excretion frequency," and it has been shown that the excretion frequency (intensity of infection) is directly related to the loss of function and degree of pathological change in this organ. In eight alimentary carriers in a mental institution the removal of the gall-bladder and treatment with neomycin has led to the elimination of the carrier state and a cessation of faecal excretion of the organisms. This has been accompanied by improved liver function, improved general health, psychological uplift, and the prospect of free social intercourse, group therapy, and rehabilitation. These results have been obtained without mortality or morbidity. A ninth carrier relapsed at the fourth month after cholecystectomy, but there is now good evidence that he has been cured since the relief of residual biliary stasis by further operation.

From the investigations, several interesting observations are suggested.

1. *Route of Infection.*—The infection seems to be maximal at the mucosal side of the gall-bladder wall as judged by the inflammatory reaction. This is taken as indicating that the gall-bladder is infected via the bile.

2. *Gall-bladder Lesion.*—Although Garbat's "test-tube" theory may be, and probably is, correct, there is in the series a quite definite correlation between the

excretion frequency and the degree of pathological change in the gall-bladder wall.

3. *Ducts.*—The course of the case which relapsed (Case 2) indicates that infection may persist in the ducts after removal of the gall-bladder, and especially so if there is a tendency to stasis.

4. *Extrahepatic and Extrabiliary Foci.*—There is no evidence of persistence of infection in any other site in any of the nine carriers, and no evidence to support Badia's (1941) contention that the longer the duration of the carrier state the more likely is the infection to have progressed to the ducts and liver.

5. *The True Intestinal Carrier.*—There is no evidence in the findings to support the view that the true intestinal carrier exists.

6. *Gall-stones.*—The absence of gall-stones is not a contraindication to operative treatment. The incidence of gall-stones in this series suggests that they arise secondarily in chronic carriers, but the first case illustrates the fact that a high excretion frequency and advanced histological changes can occur in a chronic carrier of long standing without the production of stones.

7. *Urinary Overspill.*—The observation of Browning *et al.* (1933) that bacilli occasionally occur in the urine of chronic alimentary carriers was confirmed.

8. *Danger to Carriers from this Latent Infection.*—That the carrier state constitutes a potential danger to the carrier as well as to the community is shown by the fact that the first patient developed an obstructive jaundice, and that three of the carriers had gall-stones and some had attacks of cholecystitis or cholangitis. There seems to me at least as much justification for advising cholecystectomy in chronic alimentary carriers as for advising the operation for chronic gall-bladder disease in the general population.

9. *Surgical v. Medical Measures.*—Efforts to cure the chronic alimentary enteric carrier state have covered a wide field of therapy, and with the discovery of modern chemotherapy and antibiotic agents it seems to have been assumed that it would only be a matter of time before the carrier state could be eliminated by their use. Time, however, passes, and still there are foci of carriers from whom the general medical conscience is conveniently shielded. For them, hope of cure is receding, and it is my belief that they should be promptly afforded the benefits of surgical treatment.

10. *Laboratory Aids.*—The most useful of the various tests which have been employed in the pre- and post-operative investigation of this group of patients have been (1) the serum bilirubin, which showed a higher value in the carriers with a high excretion frequency and a fluctuating and rising post-operative course in the patient who relapsed; (2) the E.S.R., which remained high in the patient who relapsed; and (3) the Widal reaction.

11. *Antiseptic Masking.*—The possibility of masking the carrier state by the use of efficient intestinal antiseptics should be borne in mind.

Carrier Problem in Scottish Mental Hospitals and Abroad

In view of the successful results in the Bellsdyke series of carriers, I carried out a survey to determine the extent of the problem in Scottish mental hospitals. Inquiries were addressed to the superintendents of 38

hospitals and institutions. Thirty-six replies were received, and the following list indicates the numbers of carriers found in three situations:

Baldovan Institution, Dundee	18
Craig Dunain Hospital, Inverness	7
Hawhead Hospital, Glasgow	12
	<hr/>
	37

An indication of the extent of the carrier problem abroad is given by the following figures in the literature.

		Estimated No. of Carriers
1937 ..	Baltimore ..	158
1947 ..	Washington State ..	38
1948 ..	" ..	44
1957 ..	Ireland ..	285

It is suggested that the benefits of the methods outlined in this investigation be extended to other carriers, many of whom are subjected to restriction and anxiety and all of whom harbour potentially serious disease.

Summary

Nine chronic alimentary enteric carriers in a mental hospital have been treated by cholecystectomy and neomycin therapy. In eight cases the carrier state is believed to have been eliminated. In the ninth carrier an overt relapse occurred at the fourth post-operative month, but investigations carried out in the intervening months suggested that his infection was persistent; indeed, his relapse was predicted. After further operation and treatment he is believed to be cured. The results have been obtained without mortality or morbidity.

Radiological, biochemical, bacteriological, and histological investigations have shown that the gall-bladder and bile-duct system are the seat of the persistent infection which is responsible for the alimentary carrier state, and that the degree of infection is proportional to the excretion frequency.

The literature of the past 50 years has been reviewed and a comparison made of the results of surgical and modern medical treatment.

A plea is made for the wider application of this method of treatment.

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SERUM PROTEINS AND HEPATIC FUNCTION IN PREGNANCY WITH ANAEMIA IN NIGERIAN WOMEN

BY

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In Nigeria, as in several other parts of Africa, anaemia is a frequent complication of pregnancy (Lawson and Lister, 1955). The management of this anaemia has been greatly influenced by the view that it is the result of protein malnutrition and of nutritional liver damage (Woodruff, 1951, 1956).

There is, however, very little information available about liver function and the incidence of protein malnutrition syndrome in pregnant Nigerian women.

Significant changes take place in the serum protein pattern in severe protein deficiency in children (Anderson and Altmann, 1951; Edozien, 1960) and in adults (Peters *et al.*, 1927; Denz, 1947; Walters *et al.*, 1947), the most important findings being hypoproteinaemia and hypoalbuminaemia. The serum protein changes provide a more sensitive index of protein deficiency than haemoglobin concentration, a point clearly shown by the fact that hypoproteinaemia and hypoalbuminaemia are invariable in kwashiorkor, while anaemia is found in only a proportion of cases and severe anaemia is unusual (Trowell *et al.*, 1954; Foy and Kondi, 1958). Protein deficiency of a degree sufficient to cause severe anaemia in pregnancy should therefore be associated with highly significant differences in total protein and in albumin concentration between anaemic and non-anaemic pregnant women.

In this paper we record observations on the serum proteins and on liver functions of pregnant Nigerian women, with and without anaemia.

Materials and Methods

The pregnant subjects were Nigerian women, mostly of the Yoruba tribe, who attended the antenatal clinics at University College Hospital and Adeoyo Hospital, Ibadan, in January to December, 1958. All the non-anaemic women had haemoglobin concentration of 10 g./100 ml. (68%) or over throughout pregnancy,

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while the anaemic patients had haemoglobin levels of less than 10 g./100 ml. at the time of investigation. Some of the pregnant women, both normal and anaemic, had other complications, such as disproportion, which were not thought to have altered the blood picture. Electrophoresis of haemoglobin was done on all the pregnant women, and those with two abnormal genes have been excluded from this series.

The non-pregnant adult women were healthy volunteers, being part of a group of adults who were being used to establish normal biochemical values in Nigerians.

Haemoglobin and haematocrit were estimated by standard techniques as described by Dacie (1956). Plasma iron was determined by the method of Bothwell and Mallett (1955).

For haemoglobin electrophoresis, haemolysates on Whatman No. 3 MM. paper were subjected to a direct current of 0.34 mA/cm. at 200 volts for 15–17 hours, using barbitone buffer (pH 8.6 and ionic strength 0.05).

Marrow was aspirated from the left iliac crest and the smears were stained with May-Grünwald and Giemsa stains (Dacie, 1956).

The analytical procedures adopted in this investigation for total proteins and the protein fractions and for liver-function tests have been reported previously (Edozien, 1958a).

Haematological Data

Anaemic Subjects

The haematological data on the anaemic pregnant women are shown in Table I. There were 24 women with a severe degree of anaemia (haemoglobin of 4 g./100 ml. or less), 22 with haemoglobin between 4.1 and 7.9 g./100 ml., and 30 mildly anaemic pregnant women whose haemoglobin was between 8 and 9.9 g./100 ml. at the time of investigation.

TABLE I.—Haematological Data on Anaemic Pregnant Women

Haemoglobin (g./100 ml.)	No. of Cases Investigated	Bone-marrow Findings	
		Megaloblastic	Normoblastic
2.5–4.0 ..	24	17	7
4.1–7.9 ..	22	3	7
8.0–9.9 ..	30	—	—
Total ..	76	20	14

The mean corpuscular haemoglobin concentration was between 26% and 35%. Ten patients had a M.C.H.C. of less than 29%: in seven of these who had not previously received therapeutic iron the plasma iron level, except for Case No. 16826 (Table IV), ranged from 74 to 213 µg./100 ml. (normal values: 50–250 µg./100 ml.).

The bone-marrow was examined in 34 cases. This investigation was made in all 24 patients having haemoglobin concentration of 4 g./100 ml. or less, and 17 (70.8%) had megaloblastic erythropoiesis.

Haematological Response to Treatment

Because of the severe degree of anaemia, many patients had to have blood transfusion. In the most severely anaemic women it was necessary to give red cells without increasing the total blood volume ("exchange transfusion"), and such patients were initially treated by a simultaneous infusion of 1,000–1,500 ml. of concentrated red cells and venesection of 1,200–1,700 ml. (W. T. Fullerton, 1960, personal communication).