to a similar conclusion. Ovarian tumour, constriction ring, or breech or face presentation were not observed, although Freeth found one of each abnormality.

A maternal mortality of 2% and a foetal loss of 28% are similar to Freeth's figures. In the last 25 cases reviewed the total foetal loss was only 8% and all the mothers survived.

Reference to Table VII demonstrates the progressive improvement in the maternal mortality since 1928. Analysis of the deaths in Miller's series suggests that the reduction

TABLE VII.—Review of Earlier Series

Author	Location	Year	No. of Cases	Maternal Loss %	Foetal Loss %	Minimal Foetal Loss %	No. of Ruptured Uteri
Gadd.	Manchester,	1952	100	2	28	14	2
Freeth	Birmingham,	1950	100	2	34	10	—
Feeney*	Dublin,	1947	77	16.9	60	56	6
Munro	Glasgow,	1933	70	7	51	?	?
Kerr							
Stacey	Sheffield,	1931	154	15	52	29	?
Miller	{ Manchester Glasgow Edinburgh }	1928	558	10	64	23	8

* Does not include any cases in which normal delivery or low forceps with-out complications to the mother occurred.

in maternal loss is due to the advent of antibiotics and blood transfusion rather than to greater obstetrical skill. Miller's deaths occurred from sepsis (37), ruptured uteri (8), post-partum haemorrhage and shock (6), pneumonia (3). Excluding the deaths from sepsis and pneumonia, maternal deaths were only 2.5%, a figure similar to the two recent series in which none of the four deaths occurred from sepsis.

A similar reduction occurred in the total foetal loss. The minimal foetal loss is the percentage of babies dead on admission. Excluding Feeney's series there has been a change for the better in the type of case. In Miller's and Stacey's series the babies dead on admission were over twice as many as in the two later series. Subtracting the minimal foetal loss from the total foetal loss gives the "actual" loss of babies in hospital. In Stacey's series this was 23% and in the present series 14%. This difference may be accounted for by the more confident and safer use of caesarean section to-day for inertia, brim disproportion, and difficult occipito-posterior positions. Caesarean section was employed only for brim disproportion in Freeth's series, with the result that his "actual" foetal loss in hospital was 24%—1% higher than Stacey's figures 20 years previously.

Summary

A review has been undertaken of 100 consecutive failed forceps cases admitted to St. Mary's Hospital, Manchester, during 1943–51.

The incidence of such cases fell from 3.2% to 0.5% of the total emergency admissions, and reasons for this decline are suggested.

The commonest cause of failure was the undilated cervix (39%).

The maternal mortality was 2% and the total foetal loss was 28%.

Pyrexia was notifiable in 18% of the cases.

A comparative survey of earlier series is presented, and reasons are suggested to explain the gradual improvement noted in the results.

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BIBLIOGRAPHY

- Feeney, J. K. (1947). *Irish J. med. Sci.*, p. 190.
 Freeth, H. D. (1950). *British Medical Journal*, 2, 18.
 Hendry, J. (1928). *Ibid.*, 2, 185.
 Kerr, J. M. M., and Moir, J. C. (1949). *Operative Obstetrics*, 5th ed., p. 467. London.
 Miller, D. (1927). *British Medical Journal*, 2, 685.
 — (1928). *Ibid.*, 2, 183.
 Shaw, Sir William Fletcher (1928). *Ibid.*, 2, 188.
 Stacey, J. E. (1931). *Ibid.*, 2, 1073.

CRISES IN CONGENITAL SPHEROCYTIC ANAEMIA (ACHOLURIC JAUNDICE)

BY

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Since the observation by Owren in 1948 that in the crisis of "acholuric jaundice" the bone marrow showed hypoplasia of the erythron there have been confirmatory reports in America (Dameshek and Bloom, 1948) and on the Continent (Cremers, 1950; Gasser, 1950). Other than an annotation in the *British Medical Journal* (1949) there has been extremely little comment in this country. Whitby and Britton (1950) merely note Owren's views without comment. Changes in the bone marrow as a cause of "crisis" have by no means reached general clinical assent.

Details of the marrow changes in four crises in three children are presented here, and the probable aetiology of the anaemic crisis is discussed.

Case 1

The patient was first admitted to hospital at the age of 1 month with extreme pallor and a history of icterus neonatorum lasting 20 days. Her haemoglobin was 5.2 g.% and she was thought to be a case of congenital hypoplastic anaemia. A blood transfusion was given and she was discharged. When readmitted two months later with further anaemia (Hb 5.6 g.%) her reticulocytes varied between 2.5

FIG. 1.—Case 1. Showing changes in haemoglobin and reticulocyte level during the first crisis. M=marrow biopsy.

and 4% of 2,250,000 red cells. Spherocytes were seen in the film. She was given a further transfusion and discharged.

She attended the out-patient department for about a year, during which her haemoglobin remained around 8 g.% and her reticulocytes between 3 and 6%.

She then had a crisis. This followed a period of restlessness, fretfulness, cough, and nasal discharge for two weeks, during which time she was seen to become increasingly pale. The course of the crisis may be seen in Fig. 1. No reticulocytes were seen for five days; they then appeared, and increased steadily in numbers over the next nine days, her general condition then returning to the pre-crisis state. Marrow biopsies were taken at the onset of the crisis and after recovery. Marrow pictures were based on counts of

approximately 1,000 cells; the cells were:—*At crisis*: myeloblasts, 1.0; promyelocytes, 4.0; neutrophil myelocytes, 7.75; eosinophil myelocytes, 0.25; neutrophil metamyelocytes, 8.0; eosinophil metamyelocytes, 0.25; neutrophil polymorphs, 18.5; eosinophil polymorphs, 1.25; basophil polymorphs, nil; lymphocytes, 13.0; mononuclears, nil; proerythroblasts, 3.0; eosinophil normoblasts, 2.0; intermediate normoblasts, nil; late normoblasts, nil; unidentified cells, 2.0; haematogones, 37.0; plasma cells, nil; reticulo-endothelial cells, 1.0; mitotic cells, 0.25. *After recovery from crisis*: myeloblasts, 0.25; promyelocytes, 1.25; neutrophil myelocytes, 7.0; eosinophil myelocytes, 1.0; neutrophil metamyelocytes, 9.0; eosinophil metamyelocytes, 0.25; neutrophil polymorphs, 4.5; eosinophil polymorphs, 0.75; basophil polymorphs, 0.25; lymphocytes, 6.0; mononuclears, nil; proerythrocytes, 3.25; early normoblasts, 11.0; intermediate normoblasts, 22.0; late normoblasts, 29.25; haematogones, 2.5; plasma cells, nil; reticulo-endothelial cells, 1.0; mitotic cells, 0.75.

The distribution of primitive cells in the erythron (Fig. 2) shows a general depression in the crisis period.

FIG. 2.—Case 1. First crisis. Showing the percentage of cells of the erythroid series seen in the marrow during the crisis period and later in the recovered state ("usual").

marrow again showed hypoplasia of the erythron. Her erythrocyte count fell from 3,800,000 to 2,500,000 in five days, the haemoglobin from 8.2 to 5.5 g.%, and the reticulocytes from 133,000 (3.5%) to 35,000 per c.mm. (1.4%). Her reticulocytes remained low for the next four days and then steadily rose during the next week to 350,000 per c.mm. and the blood count steadily returned to its pre-crisis level of between 8 and 9 g. Hb% with 4,000,000 to 4,500,000 erythrocytes. Her marrow again showed hyperplasia of the erythron—that is, the changes seen in the previous crisis were repeated.

Her spleen was then removed. Since that time her haemoglobin has remained in the order of 10 to 12 g.%, and she has shown no anaemic crisis.

Other Investigations.—During her anaemic crisis no changes were seen in her leucocyte count. Erythrocyte saline fragility curves showed haemolysis commencing in 0.67% and complete in 0.4% saline. Coombs's test was negative. The serum bilirubin during the second crisis was 1.3 mg. per 100 ml., a single level done in a quiescent phase being 1.1 mg. per 100 ml. The child's mother has a spherocytic anaemia with abnormal saline fragility, but gives no history of recurrent anaemic crises.

Comment.—This child, who had typical familial spherocytic anaemia, was observed through two crises. Both episodes were preceded by a clinical disorder, the first by an upper respiratory infection, and the second by an intestinal disturbance which may have been an infection. In both crises the usually hyperplastic erythron was replaced by extremely hypoplastic tissue and there was a great fall in peripheral reticulocytes. The first crisis was severe, and was associated with a depression of the bone marrow which lasted at least 10 days. The second crisis was much less severe, and the duration of the hypoplasia seemed to be less. In both instances

recovery was spontaneous. No depression was seen in the leucon either in the peripheral blood or in the bone marrow. During the crisis the child was pale and yellowish but not notably jaundiced, and the blood bilirubin did not appear significantly raised from the resting level. Splenectomy effected a clinical cure.

Case 2

This child was admitted in "crisis" at the age of 6½ years. She had been one of twins and had had spastic quadriplegia since birth. No history of anaemic episodes was available.

Examination revealed severe pallor, Hb 3.4 g.%, R.B.C. 1,300,000, and reticulocytes 5,200 per c.mm. The erythrocytes showed marked spherocytosis. Her saline fragility curve was typical of hereditary spherocytic anaemia; haemolysis began in 0.75% and was complete in 0.40% saline. No evidence of serological blood incompatibility was found. Her bone marrow on admission showed considerable depression of erythropoiesis, particularly in the late normoblast stage (Fig. 3).

Immediately after the marrow puncture she was given a blood transfusion; this raised her haemoglobin to the region of 10 g.%, and coincidental with this her reticulocytes rose to 224,000 per c.mm. and remained at about this level for several days.

Marrow puncture at this time showed hyperplasia of the erythron and a picture similar to that seen in subsequent studies before splenectomy.

The leucocyte counts throughout the crises were above what appeared to be a normal level for the child.

She was subsequently discharged for a few weeks and then readmitted for splenectomy, after which her reticulocyte count fell to normal levels, although her fragility curve remained abnormal. She has since then shown no anaemia. Faecal bilirubin excretion during the period of crisis was 19 mg. a day. Later when she came in for splenectomy the level was 62 mg. a day.

Comment.—We were unable to follow the whole course of the crisis in this child. She showed, however, three features: (1) reticulocytopenia and marrow hypoplasia during the crisis; (2) an apparent immediate reticulocyte response to the administration of 2 pints (1,140 ml.) of blood; (3) a relative diminution of faecal bilirubin excretion during the crisis period.

Case 3

This child was first seen when aged 6 years, and was admitted with a history of increasing pallor for about 48 hours. She was extremely pale with a faint yellowish tinge. Her blood bilirubin was 1.8 mg. per 100 ml. Her haemoglobin was 1.3 g.%, R.B.C. 900,000, platelets 47,000 per c.mm., and reticulocytes 14,000 per c.mm. Her erythrocytes showed marked spherocytosis and increased saline fragility. (Haemolysis began in 0.75% and was complete in 0.40% saline.) Her bone marrow showed extreme hypoplasia of the erythron with a few giant proerythroblasts.

A blood transfusion given immediately after the marrow puncture produced a dramatic change in her appearance. Before the transfusion it was a point of bedside discussion whether or not she was icteric; after the transfusion she looked so like the other children in the ward that the question of icterus did not arise.

FIG. 3.—Case 2. Showing the percentage of primitive cells of the erythron in the bone marrow during the period of crises and after the recovery from the crises.

Her subsequent course is illustrated in Fig. 4. Her platelet count rose within six days to her normal figure, while her reticulocyte count did not rise until several days later.

FIG. 4.—Case 3. Showing the changes in reticulocytes, platelets, and haemoglobin during the crisis. Blood transfusions were given at the points marked B.T.

Later marrow studies showed hyperplasia of the erythron (Fig. 5). Bilirubin studies could not be carried out. Her mother's erythrocytes showed increased fragility in saline, but she gave no history of anaemic crises.

After the child's spleen was removed her reticulocytes fell from their apparent usual level of 200,000 to 8,000 per c.mm. Her haemoglobin remained around 14 g.%. She has since then shown no clinical symptoms.

FIG. 5.—Case 3. Showing the percentage of primitive cells of the erythron in the bone marrow during the crisis and after recovery from the crisis.

serum bilirubin, giving her a mild yellow tinge. After transfusion this disappeared. Her marrow showed extreme hypoplasia of the erythron during the crisis, compared with hyperplasia in her usual state. The return of platelets in her peripheral blood preceded the return of reticulocytes. The latter may have been postponed by the adequate blood transfusion.

Discussion

In the three children described here four crises were seen. All of these crises were associated with a reticulocytopenia in the peripheral blood and a period of hypoplasia of the erythroid element of the bone marrow. In the case most carefully studied the two crises were preceded by a period of symptoms suggesting an infection and both crises resolved spontaneously. The other two cases showed more severe anaemia and required blood transfusion. From a biochemical point of view the one case in which faecal bile elimination was studied showed diminished excretion during the crisis period, and in one other case the blood bilirubin was not significantly raised during the crisis.

Owren (1948), in a study of six cases of crises in acholuric jaundice, saw reticulocytopenia in five of them. In one case he followed the marrow picture through the complete crises. He observed that in the crises the red blood cell count fell to about a half of the original level in about six

days. He noted a reduction in serum bilirubin and diminution in urinary urobilin excretion. In the bone marrow he saw a spontaneous recovery of the erythron, beginning on the ninth day of crises. He considered that the aplastic phase of the bone marrow was able of itself to account for the blood changes during the crises. The finding of marrow aplasia during the period of crises was confirmed by Dameshek and Bloom (1948), but they considered the crises to be due to a phase of hypersplenism in which the spleen produced an inhibitory effect on the bone marrow and at the same time itself increased its own haemolytic activity. The aplastic factor in the crises was also confirmed by Gasser (1950), Cremer (1950), and Hermansky (1951). Schrumpf (1950) summarized a group of papers read at the Société Européenne d'Hématologie at Montreux by saying "... it is advised to remove the statement from most textbooks of increased reticulocytic number during haemolytic crises. What really happens is that the number is lowered during the crisis."

It was soon noted that similar aplastic crises occurred in sickle-cell anaemia (Singer, Motulsky, and Wile, 1950; Chernoff and Josephson, 1951). In this condition hypersplenism does not seem to occur and removal of the spleen does not influence the course of the disease.

In discussing the cause of the anaemic crises the most important single factor would seem to be the length of life of the individual cell. It has been shown that whereas the life of a normal red cell is about 100 days that of a red cell in a case of hereditary spherocytosis is about 14 days (Dacie and Mollison, 1943; Owren, 1948). Thus if there was an absolute cessation of red cell production for a period of 10 days in a normal person the effect on the peripheral blood would be a reduction of about 10% of the peripheral count for 100 days. In a case of spherocytosis, on the other hand, a similar cessation of cell production would result in a precipitous fall in red cells. If the aplasia lasted 14 days it would theoretically result in there being no peripheral surviving cells at all. It is this feature which would seem to account for the presence of anaemic crises in spherocytic and sickle-cell anaemia.

Clinically the crises often appear to have a very rapid onset, but this is compatible with the view that the anaemia is due to aplasia. The clinical acute pallor will be associated with a fall of haemoglobin from the regions of 5 g. to around 3 g. This can easily occur owing to the elimination by the spleen of surviving spherocytes in 36 to 48 hours. It is interesting to observe that in Case 1 of our series the two crises were of different severity, the second crisis being much less severe than the first. The milder crisis was associated with a less marked reticulocytopenia.

Three mechanisms that need discussion in the production of the crises are (1) the role of increased haemolysis, (2) hypersplenism, and (3) marrow aplasia.

There is virtually no evidence of increased haemolysis in cases recently studied and reported during crises. No increase in bile excretion occurs. Owren noted an absolute diminution in jaundice and blood bilirubin during the crises. The name "acholuric" attached to the disease is on simple clinical observation that in this type of jaundice an increase in bile elimination does not occur. The theory of two forms of bilirubin used to explain the anomaly is probably false (Gray and Whidborne, 1947).

The role of hypersplenism was largely adopted by Dameshek and Bloom; they had no evidence that the spleen itself produces the marrow aplasia. They noted a relative increase in the number of spherocytes in the peripheral blood during crises and suggested that this was due to splenic activity. A more likely explanation is that in crises there is a relative increase in older and hence spherocytic cells. The presence of aplastic crises in sickle-cell anaemia, in which hypersplenism does not seem to occur, necessitates a different explanation of the crises in the two similar diseases. Further, Freund (1932) refers to cases in which splenectomy did not prevent later death from anaemia.

The evidence suggests that the aplasia of the erythron can itself account for the clinical presentation of an anaemic crisis. In that case why the aplasia?

It has been considered that the crises in spherocytic anaemia are often precipitated by infection (Murray-Lyon, 1935; Scott, 1935; Dameshek, 1941; Horne, Lederer, Kirkpatrick, and Leys, 1945), and recently it has been recognized that certain infections, notably diphtheria and infectious mononucleosis (Gasser, 1950; Chernoff and Josephson, 1951), may be associated with a transient hypoplasia of the erythron.

In spherocytic anaemia we have to consider the effect of an infection upon a bone marrow in a state of prolonged and profound compensatory hypertrophy and therefore especially liable to a conditioned nutritional deficiency. The diversion of essential protein which is thought to be responsible for the anaemia of infection (Cartwright and Wintrobe, 1952), could thus be exaggerated in effect, and a relatively acute deficiency could occur, with resulting aplasia.

Such an explanation would seem to us more likely than the postulation of a hypothetical hypersplenism, and would also account for the apparently increased tendency to crises during pregnancy.

Summary

Four crises in three children with spherocytic haemolytic anaemia were studied.

All crises were associated with reticulocytopenia and with hypoplasia of the erythron in the bone marrow.

Recovery from crises was associated with the reformation of the usual hypertrophic marrow.

No evidence of increased haemolysis was seen in the crises.

It is suggested that the marrow aplasia is the primary cause of the anaemic crises and that the aplasia is due to conditional deficiency states induced by the presence in the body of an infection on a marrow undergoing prolonged compensation hypertrophy.

We are indebted to Dr. T. Colver and Professor R. S. Illingworth, the paediatricians in charge of the cases reported here.

REFERENCES

- British Medical Journal*, 1949, 1, 228.
 Cartwright, G. E., and Wintrobe, M. M. (1952). *Advances in Internal Medicine*, 5, 165. Year Book Publishers, London.
 Chernoff, A. I., and Josephson, A. M. (1951). *Amer. J. Dis. Child.*, 82, 310.
 Cremer, J. (1950). *Sang.*, 21, 271.
 Dacie, J. V., and Mollison, P. L. (1943). *Lancet*, 1, 550.
 Dameshek, W. (1941). *New Engl. med. J.*, 224, 52.
 — and Bloom, M. L. (1948). *Blood*, 3, 1381.
 Freund, M. (1932). *Amer. J. Dis. Child.*, 43, 647.
 Gasser, C. (1950). *Sang.*, 21, 237.
 Gray, C. H., and Whidborn, J. (1947). *Biochem.*, 41, 155.
 Hermansky, M. F. (1951). *Cas. Lek. ces.*, 90, 15.
 Horne, J. L., Lederer, H., Kirkpatrick, H. J. R., and Leys, D. G. (1945). *Lancet*, 2, 33.
 Murray-Lyon, R. M. (1935). *British Medical Journal*, 1, 50.
 Owren, P. A. (1948). *Blood*, 3, 231.
 Schrumph, A. (1950). *Sang.*, 21, 139.
 Scott, A. M. (1935). *Lancet*, 2, 872.
 Singer, K., Motulsky, A. G., and Wile, S. A. (1950). *J. Lab. clin. Med.*, 35, 721.
 Whitby, L. E. H., and Britton, C. J. C. (1950). *Disorders of the Blood*, 6th ed. p. 324. Churchill, London.

The C.W.S. Retail Co-operative Society of Manchester was fined £120, with 10 guineas costs, at Hastings, Sussex, on March 18 on five summonses in respect of the condition of premises used for food storage at St. Leonards. The society pleaded guilty to summonses accusing them of (1) failing to provide a sufficient supply of water for persons employed there; (2) failing to see that the walls, ceilings, and doors of the room had been purified; (3) failing to give notice that an infestation of rodents was present in the room; (4) failing to protect food stored in the room; and (5) failing to see that the walls, ceilings, floors, and windows were kept in a proper state of repair. The premises were used for the storage of cereals, rice, and beans in sacks and packages. A spokesman for the society said they deplored this matter and now had very good premises.

FURTHER TRIAL OF AUREOMYCIN IN THE TREATMENT OF CHOLERA*

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In a previous communication (Seal, Ghosal, and Ghosh, 1951) the results of a preliminary trial of aureomycin, administered intravenously, in the treatment of cholera cases were reported. These being unsatisfactory it was suggested that the oral route might be chosen for the administration of the drug if further trial was undertaken in future. Accordingly a trial was organized in the same institution at Calcutta, this time during the prevalence of cholera epidemic in the city between April 30 and July 20, 1951. Only frankly typical cases were chosen at random and were divided into three groups: experimental, sulphaguanidine control (control 1), and saline control (control 2), the number of cases treated in each group being 50, 35, and 35 respectively, total 120. The subjects were all males and were admitted in a stage of collapse, generally within 24 hours of the onset of symptoms, and had received little or no treatment prior to admission to hospital.

Treatment

Dosage.—The drug was supplied in capsules, each containing 250 mg. In the previous study the dosage used for intravenous administration was 100 mg. every six hours, and in a few cases 50 mg. every three hours, the total quantity used being generally 300 mg. Some untoward symptoms were noted with 100 mg., but not with 50 mg. per adult dose. With this experience, and in the absence of any previous knowledge of the dose which would be suitable for oral administration in cholera patients, it was tentatively decided to try one capsule of 250 mg. every three hours. This amount was easily retained with no untoward effect referable to the drug. A few cases which showed complications during the course of the disease will be discussed later. Of the 43 cases which recovered 8 were clinically severe, 23 moderately severe, and 12 were mild, the average doses received by these groups being 6.65 g., 5.5 g., and 4.875 g. respectively. From the nature of response obtained by oral administration of the drug it appears that 500 mg. every three hours or 250 mg. every one and a half hours may be tried as an initial dose, whichever is found convenient, and if the drug is effective at all the total amount actually needed for recovery may be much less than has been used in the present investigation, perhaps about 3 to 5 g., depending upon the severity.

Other Treatments.—As in the previous trial, all cases brought to the hospital in a state of dehydration and collapse were given intravenous saline and glucose in varying

*Presented before the Medical and Veterinary Section of the Indian Science Congress Association at its annual meeting held at Lucknow in January, 1953.

†Dr. S. C. Ghosal has died since the paper was written.