HEINZ-BODY ANAEMIA IN THE NEWBORN

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Haemolytic anaemia in the newborn is usually due to the transfer of antibodies from the maternal to the foetal circulation (haemolytic disease of the newborn), but such an anaemia may also be the result of an inherent defect, such as congenital spherocytosis. A further haemolytic anaemia occurring in premature infants was reported by Gasser and Karrer (1948) and Gasser (1951, 1953). They described the clinical appearances and haematological findings in 14 infants with this condition, which they called the "spontaneous" Heinz-body anaemia.

The children developed jaundice in the first few days of life, usually between the first and fifth days. Anaemia appeared as the jaundice faded, commonly during the third week. The general condition of the infants deteriorated; they became pale, refused feeds, and were drowsy. At no time could the spleen be felt. Examination of the blood before the development of the anaemia showed the presence of Heinz bodies in 9–45% of the red cells. There were many distorted, disintegrating red cells when the anaemia was severest.

Heinz bodies are intracellular inclusions in the red cells which stain by various supravital dyes, but not by Romanowsky stains. They are thought to be particles of denatured haemoglobin. They occur in man as a result of poisoning with a variety of chemicals, but no such cause could be found in the mothers before or after birth or in the infants.

In the present paper, two unusual cases of Heinz-body anaemia are reported; one patient was a normal full-term infant and the other was not jaundiced at any time during the illness.

Methods.—Haemoglobin estimations were carried out by the oxyhaemoglobin method, using a photoelectric absorptiometer. Red- and white-cell counts were done in a Burkner counting chamber. Reticulocytes and Heinz bodies were counted in brilliant cresyl-blue and Nile-blue dry preparations, and the effect of counterstaining with Romanowsky dyes was observed after previous fixation with ethanol. Differential counts were carried out on blood smears stained with May-Grünwald-Giemsa and on bone-marrow smears stained with N.R.G. (Gurr). The osmotic fragility of the red cells was determined both before and after incubation (Varadi, 1951), using the method of Parpart *et al.* (1947).

Case 1

The patient was a full-term male infant, one of non-identical twins, normal delivery, whose birth weight was 3,370 g. (7 lb. 7 oz.). During pregnancy the mother was found to be hypertensive; she had ankle-swelling and was anaemic but not jaundiced, and she had had no known contact with any case of hepatitis. The infant fed poorly from birth and the mother noticed that the baby was jaundiced when he was two weeks old. The twin sister was perfectly

well. The child's motions were loose but not pale. As the jaundice persisted, he was admitted to hospital on October 25, 1954; he was then 3 weeks old.

On examination he was seen to be very jaundiced, quite active, and crying normally. The liver could be felt one fingerbreadth below the right costal margin; the spleen could not be felt; the stools were not pale. No abnormality was found in the cardiovascular, respiratory, and central

TABLE I.—Results of Peripheral Blood Examinations in Case 1

Date	Hb g./100 ml.	R.B.C. × 10 ⁶	Retic. %	Nucl. R.B.C.	W.B.C.	Plate- lets	Notes
Oct. 26	6.8	1.82	8.6			Normal	Numerous distorted red cells and a few microspherocytes. Heinz bodies + + + Morphology as on Oct. 26. Heinz bodies in 31% of R.B.C.s
" 27	6.2		19.4	2 per 100 W.B.C.			
" 28	4.4	1.48	23.4	1.100/c.mm	16,200	"	Heinz bodies fewer. Polychromasia more marked
" 29	14.5	4.5	12.2				Morphology reverting to normal. Heinz bodies very sparse
Nov. 2	14.5		5.2				
" 5	14.5		1.8				
" 9	13.3						
" 12	12.6						
" 16	13.6	4.3	<1

FIG. 1.—Case 1. Results of peripheral blood examination.

FIG. 2.—Case 1. Showing numerous distorted red cells and a few spherocytes. (×1,200.)

nervous systems. The following diagnoses were considered possible: (1) acholuric jaundice, (2) infection, and (3) haemolytic disease. The following haematological examinations were carried out.

Peripheral Blood (Table I, Fig. 1).—This showed the presence of a severe haemolytic anaemia; many distorted red cells and a few spherocytes were present (Fig. 2); nearly one-third of the red cells contained Heinz bodies

FIG. 3.—Case 1. Heinz bodies in nearly one-third of red cells. ($\times 900$.)

TABLE II.—Results of Tibial Puncture in Case 1

Neutrophils:		Normoblasts:	
Segmented ..	1.25%	Orthochromatic ..	0.50%
Band ..	2.75%	Late polychromatic ..	7.50%
Metamyelocyte ..	5.50%	Polychromatic ..	34.25%
Myelocyte ..	1.50%	in mitosis	
Promyelocyte ..	2.75%		
Eosinophils:		Basophilic ..	15.25%
Segmented ..	0.75%	Proerythroblasts ..	3.75%
Metamyelocyte ..	2.00%	Haemocytoblasts ..	4.25%
Myelocyte ..	1.00%	Megakaryocytes ..	0.25%
Myeloblasts ..	5.75%	Reticulum cells ..	4.00%
Lymphocytes ..	4.75%	L.: E. ratio, 0.22:1	
Monocytes ..	0.25%	Marrow cellular	
Promonocytes ..	1.00%		

(Fig. 3). In the next two days the haemoglobin fell rapidly, numerous nucleated red cells appeared, and reticulocytes increased.

Tibial Puncture on October 29 (Table II) showed an extremely active erythropoiesis with an increased proportion of early cells, findings consistent with haemolytic anaemia.

Osmotic Fragility Test.—This gave a curve with a somewhat wide span. This was due mainly to a "mode" in the range of the higher saline concentrations (Fig. 4). The mean corpuscular fragility was normal and did not show a pathological increase after 24 hours' incubation at 20° C. The tail of the curve, however, showed a marked shift to the right, caused, no doubt, by the further deterioration of the inferior distorted red-cell population on standing.

FIG. 4.—Case 1. Osmotic fragility curve in buffered solutions before (continuous line) and after 24 hours' incubation (broken line) at 20° C.

Autohaemolysis.—There was a marked haemolysis in the defibrinated blood sample after 24 hours' incubation at 37° C., weaker at 4° C.

Urobilin was strongly positive in the urine (October 27); bilirubin was negative. Serum bilirubin (October 28) was 13 mg. per 100 ml.; direct van den Bergh reaction negative. Direct Coombs test on the child's red cells was negative. Both child and mother were group O, Rh negative, and no incompatibility could be demonstrated between the mother's serum and the infant's red cells by the saline, albumin, or anti-human-globulin methods. The infant's serum did not contain abnormal cold or warm agglutinins or haemolysins. Wassermann reaction and Kahn test were negative. No pathogens were isolated from the faeces.

The child was transfused with 120 ml. of packed cells on October 29: the jaundice rapidly disappeared and was hardly noticeable after two days. The patient's condition remained good, he was gaining weight, and the motions were only slightly more watery than expected at his age. He was discharged on November 18.

Case 2

This patient was a 30-weeks, premature female infant; birth weight 970 g. (2 lb. 2 oz.). The mother's health during pregnancy was good and the delivery was normal. The

TABLE III.—Results of Haematological Examination in Case 2

Date	Hb g./100 ml.	R.B.C. $\times 10^6$	Retic. %	Nucl. R.B.C.	Heinz Bodies %	W.B.C.	Notes
Mar. 8	6.1		2.8	900	67.6	22,700	Numerous distorted red cells. Immature neutrophils ++
" 10			4.0		65.6		
" 14	4.0	1.2	18.6	6,200	55.2	15,800	
" 15	9.7	3.12	15.6	900	16.8	21,500	
" 17	12.3	4.11	18.4	800	11.6	20,800	Distorted red cells almost absent Very few immature neutrophils only
" 22	9.7		3.22	5.6		11,100	
" 29	8.7		2.86	6.4	4.4	8,200	
Apr. 5	7.7		2.5	6.0		10,800	
" 10	7.4		12.0		Few	8,900	
" 13	6.4	2.2	10.0			5,000	
" 20	7.4		9.4			5,000	

general condition at birth was good, and the child appeared to thrive until on the 13th day a soft swelling developed in the left buttock. This swelling increased gradually in size. On the 17th day it discharged spontaneously a few drops of pus and the abscess was incised three days later. About this time the child was noticed to look pale. Haematological examination (19th day) disclosed a severe anaemia (Table III, Fig. 5), with Heinz bodies (Fig. 6) and numerous distorted red cells.

The infant's general condition continued to deteriorate and she became drowsy and very pale. The haemoglobin fell to 4 g./100 ml. on the 25th day. The following day the patient was given a transfusion of 45 ml. of packed cells with very good effect clinically and haematologically. Although the haemoglobin decreased gradually during the next fortnight, Heinz-body formation ceased and haemolytic forms of red cells rapidly disappeared. The abscess healed. The child kept her feeds satisfactorily. She was never icteric and the spleen was not felt. She received no drugs.

Haematological investigations on the peripheral blood showed the

FIG. 5.—Case 2. Results of haematological examination.

typical order in which the red-cell changes develop: peak of Heinz-body formation—morphological alterations—anaemia—outpouring of nucleated red cells—peak of reticulocytes (Table III, Fig. 5).

The mother's blood was group B, Rh positive, the infant's group O, Rh negative. There were no antibodies in the mother's serum. Her Wassermann reaction was negative.

Faecal stercobilinogen (five days' average) was 4.1 g. a day. There was no increase in the urinary urobilin.

The bacteriological examination of the abscess (culture) showed a growth of *Bact. coli*.

FIG. 6.—Case 2. Showing presence of Heinz bodies. ($\times 1,100$.)

Discussion

For several reasons we felt justified in recording our two cases. Firstly, as a contribution to the differential diagnosis of haemolytic anaemias in the newborn; secondly, and more important, to point out the excellent effect of transfusion in this type of haemolytic anaemia, because if left untreated the patient may die; and thirdly, to our knowledge the condition has not previously been reported in a normal full-term infant.

The diagnosis of Heinz-body anaemia should not cause any difficulties from the haematological standpoint: the essential thing is that one should think of this diagnosis when faced with a non-obstructive type of jaundice in the first days of life. The patients are not anaemic at birth (Gasser, 1953). After the appearance of the jaundice the first haematological abnormality to be detected will be a rapidly increasing number of Heinz bodies in the red cells during the first and second weeks. As the Heinz bodies become more numerous, red cells that are shrunken, abnormally crenated, and the shape of broken eggshells make their appearance and anaemia develops.

There is a vast literature on Heinz-bodies, to which we refer the reader (see Dacie, 1954; Selwyn, 1955). A variety of aromatic nitro- and amino-compounds and inorganic oxidizing agents known to produce Heinz bodies are listed in reviews of the subject by Webster (1949) and Buckell and Richardson (1950). If the dose of the toxic substance ingested is sufficient to cause a haemolytic anaemia, both Heinz bodies and the above described morphological alterations of the red cells will be present. In the absence of any exogenous toxic cause, the occurrence of Heinz bodies was observed in cases of hypoplasia (Schilling, 1928; Zadek and Burg, 1930; Moeschlin, 1941, 1942) or aplasia of the spleen (Gasser and Willi, 1952), and also in splenectomized individuals (Selwyn, 1955). In such cases the Heinz-body formation is a permanent feature. There are reasons for believing that the spleen either filters off red cells contain-

ing Heinz bodies from the circulation or is in some way responsible for the extrusion from the cells of the bodies which are subsequently phagocytosed by the spleen.

The spontaneous occurrence of Heinz bodies was observed in the newborn in the absence of any exogenous toxic influence and without a demonstrable splenic pathology (Willi, 1947). Out of 1,251 newborn infants, 225 (18%) were found to contain Heinz bodies in over 2.1% of the red cells, and 84% of these 225 infants were premature (Willi and Hartmeier, 1950). Unlike the haemolytic anaemia with spontaneous Heinz-body formation (Gasser and Karrer, 1948; Gasser, 1951, 1953), there were neither disintegrating red cells present in these cases nor signs of an increased haemolysis or of any degree of anaemia.

As Heinz bodies are insoluble in water and red cells "tagged" with them show an increased resistance to lysis by hypotonic saline, the above clinical observations and *in vitro* tests on our Case 1 (saline fragility curve, auto-haemolysis test) suggest that the increased haemolysis is due to the presence of the irreversibly contracted distorted red cells.

No satisfactory explanation for the production of Heinz bodies has been found hitherto in the spontaneous Heinz-body syndrome of the newborn. Gasser (1953) suggested that it might be due to a "disturbance of adaptation" ("Anpassungsstörung") of the erythropoiesis in premature infants, and left the question open of whether a fault in haemoglobin synthesis or in the mechanisms normally protecting the erythrocytes from damage or a dysfunction of the spleen is to be blamed. There is a high proportion of twin pregnancies among these cases of anaemia. Five out of Gasser's (1953) 14 premature infants and our first patient were twins.

It would appear that the unknown endogenous factor causes not only Heinz-body formation and disintegration of red cells but also a depression of the erythropoiesis at the time when the changes in the mature red cells in the periphery are the severest (Gasser, 1953). According to Gasser the jaundice is haemolytic and sometimes in part also hepatic in origin. The absence of jaundice in our Case 2 is not surprising in spite of the presence of a severe anaemia associated with morphological alterations of the red cells. Jaundice need not necessarily develop if the function of the liver is unimpaired and the erythropoiesis is depressed to a sufficient degree. Such is the case in the aplastic crisis of acholuric jaundice. It is doubtful whether in Case 2 the abscess of the buttock played any part in the causation of the Heinz-body anaemia; this possibility cannot be ruled out entirely, but is unlikely.

Summary and Conclusions

Two cases of spontaneous Heinz-body anaemia are described. One, a full-term twin of normal birth weight, had both haemolytic anaemia and jaundice. The other, a premature infant, had typical haematological findings, but no jaundice. Both responded well to a single transfusion.

The haematological findings are discussed.

In the differential diagnosis of jaundice in the newborn, Heinz-body anaemia should always be considered, especially if jaundice—not obstructive in character—develops after the first day of life, the Coombs test is negative, and no immune antibodies are present in the maternal serum. It would also appear that Heinz-body anaemia (Case 2) can be present without clinical jaundice: if marked anaemia develops in the premature infant during the second or third week and contracted irregularly crenated erythrocytes are found in the smears, Heinz bodies should be looked for. It is likely that, if these haematological criteria are systematically sought, more cases of this type of haemolytic anaemia will be recognized in the future.

Heinz-body anaemia of the newborn is not only of theoretical but also of considerable practical importance, as transfusions performed in time might save life.

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SOME OBSERVATIONS ON OUT-PATIENT PSYCHOTHERAPY

WITH A FOLLOW-UP OF 235 CASES

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In the minds of most doctors the results of psychotherapy are still clothed in a certain amount of mystery. Yet with the development of the Health Service and the consequent increase in out-patient work it is important to try to estimate the value of this type of treatment. Several questions immediately spring to mind. "Is psychotherapy any good at all?" And if the answer is "Yes," then "How good?" And again, "What sort of cases should it be reserved for?"

Few papers seem to have been written on this subject, and only two will be quoted, both of which are pre-war. In 1935 Luff and Garrod reviewed 500 consecutive patients treated with psychotherapy at the Tavistock Clinic, all of whom had finished treatment at least three years previously. This is a creditable follow-up period, and the patients had had thorough treatment; indeed, half of them had between 20 and 60 interviews. The follow-up was based on information obtained from replies to letters sent out to the patient or the patient's practitioner, though occasionally other methods were used, such as a visit from a psychiatric social worker. Yet it was possible to contact only 70.4%, and there must be serious limitations to the value of a follow-up where only two-thirds of the series were contacted by letter and no patient was personally interviewed by a psychiatrist.

The second paper we quote is by Curran (1937), who records a follow-up of 83 patients. The psychotherapy was carried out under poor conditions (in a dental room of all places) at St. George's Hospital. The only

criterion for selection in Curran's series was that the patients were thought to present psychiatric problems by one of the out-patient physicians or surgeons who referred them to the psychiatric department. These cases were all seen by Dr. Curran at their first interview, though subsequently some were treated by Dr. Eliot Slater. Only 25 of the 83 attended for more than four sessions. It is important to note that these 83 patients represented only 40% of the total circularized. Another 40% did not reply to follow-up inquiry, and the remaining 20% of inquiries were returned "addressee untraced." 40% is a very small percentage of any group to be followed up, and, as Curran says, few deductions are possible. As in Luff and Garrod's series, no patients were interviewed by a doctor.

Present Investigation

Our investigation differed from the two investigations quoted above in that we endeavoured to interview the patients personally. Early in 1954 we studied the case papers and psychotherapy notes of 235 out-patients who had been selected by us as suitable for a course of out-patient psychotherapy from a total of 3,226 out-patients referred to us in Plymouth during the five-year period 1948-52. It should be noted that these 235 patients represented the total number who had been selected for psychotherapy. Thus a few patients had been discharged for nearly six years, while all had been discharged at least 15 months. In about 35% the follow-up period was two and a half years or more. It may be observed at this point that the recovery rates of those patients treated in the earlier years did not vary significantly from the recovery rates of the more recently treated, and also that the percentage of untraced cases did not increase with the passage of time. For the collection of documents we relied on the records department, and there is no reason to suppose that many cases were omitted or that the odd ones left out represented special types.

Before seeking to interview the patients we tried to reduce the mass of documentary information to some sort of order. This included placing each case in one of five diagnostic categories (as explained under "Diagnosis"), a procedure which we termed "diagnosis in retrospect." We also formed an opinion from the documents whether we considered the prognosis with treatment to be "good" or "moderately good," a procedure we termed "prognosis in retrospect." Briefly, the factors which weighed with us mostly in making this prognosis were: (1) intelligence (low, average, high); (2) attitude to life and previous adjustment (poor, average, good); (3) duration of symptoms (over 10 years, 1-10 years, under 1 year); and (4) effect of symptoms on function (very serious, serious, slight). We also had to define the terms we were using—for example, distributive analysis—and, lastly, we drew up a form for use at the time of the forthcoming interviews. Our results and conclusions were eventually arrived at through analysing the completed forms.

Types of Psychotherapy

The various types of psychotherapy used by us were divided into two main groups: (1) Superficial—by which we mean advice, explanation, suggestion, persuasion, reassurance, and encouragement. (2) Distributive analysis—by which we mean that more use was made of analytical principles and that certain experiences in the patient's life were dealt with on analytical lines.

Abreactions with the use of injections or carbon dioxide were occasionally employed, chiefly in conjunction with the main methods just defined. What is described as superficial therapy was given in 45% of the cases, and distributive analysis in 49%, while 6% were treated mainly by abreactive methods.

We based our therapy on the assumption that if a person is tackling his life problems badly and producing neurotic