The Bulletin of the
Kandang Kerbau Hospital,
Singapore.
Vol. V—No. 1—March, 1966

Anaemia of Newborn

by

Wong Hock Boon, MBBS, FRCP (EDIN.), FRFPS (GLAS.), DCH (LOND).

DEPARTMENT OF PAEDIATRICS, UNIVERSITY OF SINGAPORE.

Physiology of Haemopoiesis

a) Haemoglobin levels

The normal range of Hb levels in cord blood is of some importance in assessing whether some pathological process affecting haemopoiesis was present in intra-uterine life, e.g. an excessive high value may indicate some degree of intra-uterine hypoxia and a low level may be due to haemorrhage or haemolysis prior to delivery. However, difficulties may arise in the estimation with regard to possible clotting of the blood specimen. The following are some of the values obtained by other workers compared with the values obtained in K.K.H.: (the rather low value obtained here may be due to dilution of cord blood with other maternal fluids).

However, if daily Hb estimations are carried out from capillary blood after birth, it is found that the Hb will rise for approximately 3 days (Gairdner, 1958) after which there will be a gradual fall till the age of about 2 months when a level of 11-12 Gm% will be reached. The immediate postnatal rise is due to haemoconcentration arising from mobilization of the excess fluid in the vascular system after birth. The subsequent fall is due to 2 factors:

1. Reduction in marrow activity, and
2. Rate of growth, which, of course, is maximal at this period of life.

After 2 months of age, the marrow becomes stimulated by the low level of Hb so that this level is maintained, and depending on the availability of haemopoietic substances, the Hb will be main-

	No. Observation	Mean Hb. Gm%
Mackay (1957)	60	17·4
Guest & Brown (1957)	59	17·1
Marks, Gairdner & Roscoe (1955)	221	16·9
Rooth & Sjostedt (1957)	424	16·7
Mollison & Cutbush (1951)	134	16·6
Sturgeon (1956)	77	15·7
Chalmers, Smith & Worssam (1957)	280	15·4
Wong (1965)	100	14·4

tained, will rise or even fall. This, then, is the behaviour of the Hb levels in infancy which is conditioned by physiological processes obtaining at birth and subsequently.

b) Foetal Hb

In foetal life, the greater portion of the Hb is foetal in type, i.e. HbF. Adult Hb is detectable at about the 13th week of intra-uterine life, so that at birth the Hb of the newborn infant consists of about 58% foetal type and the rest is adult Hb. HbF values fall rapidly after birth so that by 1 month it is 37% and by 6 months it is only 2%. After the age of 1 year, the HbF value is less than 1% and the type of Hb is almost totally adult. Fig. 1 depicts the levels of foetal Hb obtained here at different age groups in

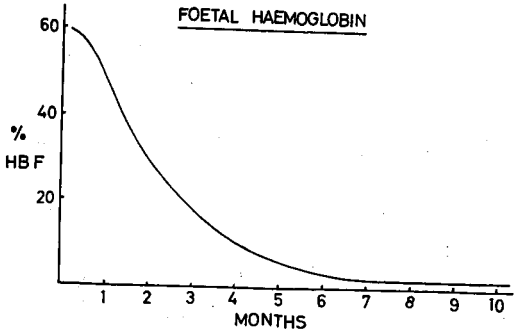

FIG. 1. Showing the amount of foetal haemoglobin at various periods in infancy. The figures were obtained from studies in 1,154 infants. Note that by 7 months Hb F is less than 1%.

infancy, figures being obtained from 1154 infants.

The possession of foetal haemoglobin in infancy does not seem to have any significant effect in the production of anaemia, as studies in the life span of red cells with foetal Hb have shown no significant differences from cells with adult Hb. (Gairdner, Marks & Roscoe, 1952).

c) Haemopoietic activity during infancy

It is essential to know the degree of activity of the haemopoietic organs during infancy in order to understand the mechanism of the production of anaemia. Hb estimations during infancy have shown a rise of Hb during the first

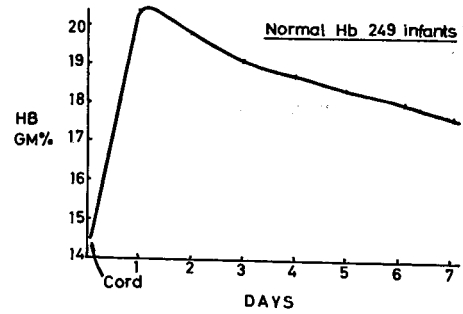

FIG. 1a. Showing the Hb levels in 249 infants in the first week of life. Note the high levels in the first 3 days and a gradual fall later.

3 days after which there is a precipitous fall in about 2 weeks when the Hb reaches the same level as in cord blood (Fig. 1a). After this there is a gradual fall to a level of 12 Gm% by the end of the 2nd month. The rise in the first 3 days is due to haemoconcentration as mentioned above, and the fall to the low level of 12 Gm% is due to 2 factors, viz. the increase in blood volume due to growth and the depression of haemopoiesis at this age. This reduction in haemopoietic activity can be demonstrated in 2 ways:-

a) Fall in reticulocyte count to $< 1\%$

b) Reduction in the marrow erythroid count.

After 2 months, the Hb concentration may rise again as the marrow activity is stimulated by the relative anoxia from the low level of Hb. This rise will only occur if sufficient iron stores are available.

Mechanism of Anaemia Production

Anaemia is a state whereby the Hb level falls and in the infant as well as the adult, the mechanism of production of anaemia depends on an understanding of haemopoiesis. The various building blocks for Hb production, such as (Fig. 2) iron, protein, etc. are delivered to the marrow which is the factory for the production of Hb. These erythrocytes with their complement of Hb are then delivered from the factory to the circulation where Hb exerts its function of oxygen carriage to the tissues. The erythrocyte has a life span of approximately 100 days when it is destroyed in the reticulo-endothelial system

from which the iron is made available for resynthesis of Hb, and the cycle will result in anaemia.

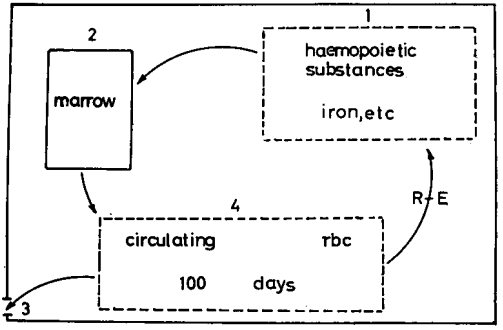

FIG. 2. Simple schema for haemopoiesis. Abnormolities in the various sections produce the following types at anaemia — 1. Dyshaemopoietic, 2. Aplastic, 3. Haemorrhagic, 4. Haemolytic.

Classification of Anaemia

On this basis, anaemia can therefore be simply classified as follows:-

1. Lack of haemopoietic substances

a) Iron—iron deficiency anaemia

b) Folic acid—megaloblastic anaemia

2. Aplastic anaemia

This is due to bone marrow failure which may be genetic or acquired.

3. Haemorrhagic anaemia

Bleeding from the vascular system either into the body or outside the body will naturally lead to a loss of available Hb with resultant anaemia.

4. Haemolytic anaemia

Reduction in the normal life span of the erythrocyte will lead to what is termed a haemolytic anaemia.

The Anaemias of the Newborn

A. Haemorrhagic Anaemia

Anaemia due to bleeding in the newborn is best subdivided into 2 groups, viz. the occult and the manifest. The former is bleeding which is not evident while in the latter, signs of bleeding are easily seen.

a) Occult

1. *Placental haemorrhage:* It had previously been assumed that bleeding prior to or at delivery always involves loss from the maternal circulation. However, it is obvious that bleeding from the placenta can equally involve loss from the foetus. Therefore, whenever so-called ante-partum haemorrhage occurs, this blood should be tested for the presence of foetal haemoglobin by its reaction with alkalis and this will differentiate adult Hb from a mixture of adult and foetal Hb. The circumstances under which foetal blood loss can occur from the placenta include:-

a) Premature separation of the placenta;

b) Abnormal position of the placenta such as placenta praevia;

c) Abnormal arrangement of the umbilical vessels such as velamentous insertion especially in combination with vasapraevia;

d) Damage to the placenta during surgical induction of labour or at caesarean section.

So far as the infant is concerned if the Hb falls below 15 Gm% in the first 24 hours of life, considerable blood loss may be presumed to have occurred.

2. *Haemorrhage from foetus into the maternal circulation:* The foetus may bleed into the maternal circulation and the infant born very pale or in shock. The possibility of such foeto-maternal transfusion can be proved by demonstrating the presence of foetal Hb in maternal blood. Zipursky et al (1959) showed that passage of red cells from the foetus into the maternal circulation occurred in 21% of so-called normal pregnancies and deliveries.

3. *Haemorrhage from one twin to another:* In monozygotic twins, blood from one twin may be transferred to the other twin, and this is due to the presence of anastomoses of the

foetal blood vessels in the placenta. Such an anastomosis may be one of the following:-

a) Artery to artery;

b) Vein to vein;

c) Artery to vein.

It is the 3rd category which predisposes to haemorrhage from one twin to the other. In such instances, one twin will be anaemic and the other polycythaemic. Dangers may be encountered in both twins, the anaemic twin may be pale and shocked, needing blood transfusion, while the polycythaemic twin may suffer from cardiac failure, or hyperbilirubinaemia, needing vevesection and exchange transfusion.

In 69 sets of twins studied in Kandang Kerbau Hospital where haemoglobin estimations were done, the incidence of the differences in Hb between the twins are shown in the following diagram (Fig. 3)

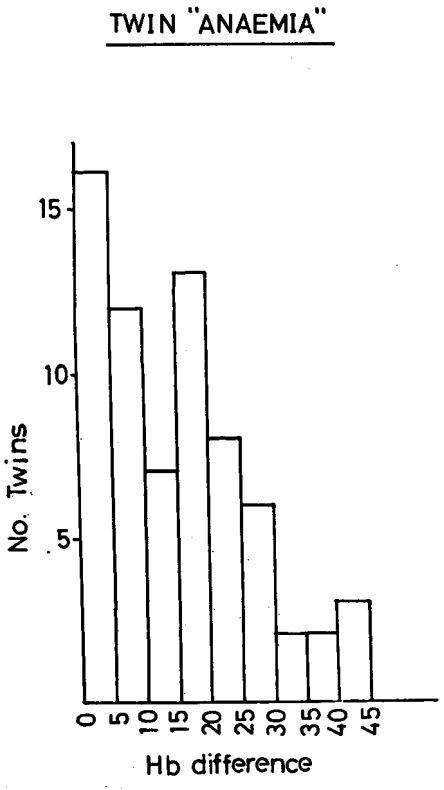

FIG. 3. The degree of Hb (expressed in %, 14.8 Gm % = 100%) difference found in 69 sets of twins.

Considering those twins where there was a difference in Hb of 1·5 Gm% or more, no significance was found in relation to the size of one twin to another or whether it was the first or second twin who had the higher or lower haemoglobin.

4. *Occult haemorrhage into body organs:* Bleeding from the liver, adrenals, peritoneal cavity, kidneys and spleen may occur from trauma during delivery especially during breech delivery.

b) Manifest

By manifest haemorrhage is meant bleeding which can easily be seen or detected by clinical examination.

1. *Haemorrhage from the cord:* Bleeding from the cord is not uncommon in Kandang Kerbau Hospital and this may occur under the following circumstances:-

a) Rupture of cord during a precipitate delivery;

b) Insecurely tied cord;

c) Loosening of the ligature in "jelly" cords;

d) Bleeding into the substance of the cord—haematomas of the cord.

2. *Haemorrhage in scalp and pericranium:* Scalp haemorrhages may superficially resemble a caput succedaneum and occur especially in infants delivered by the vacuum extractor. Cephalhaematomas may be of such a size that the infant becomes anaemic and may need a blood transfusion—there is also an added danger, namely, hyperbilirubinaemia.

3. *Manifest haemorrhage in body organs:* Intracranial and intrapulmonary haemorrhages can be detected clinically and the haemorrhage may be extensive enough to cause anaemia.

4. *Haemorrhagic disease of the newborn:* This usually is not seen immediately after birth but occurs after the 3rd or 4th days, and is due to low prothrombin or Factor V. Although theoretically, such affected infants-

may bleed from any tissue, skin haemorrhages are extremely rare. The commonest site of haemorrhage is from the gut, the infant presenting with haematemesis or malaena. However, haemorrhage may occur also in the brain, lungs and kidney. If the bleeding or anaemia is severe, blood transfusions and injection Vit. K are necessary to stop the bleeding while in mild cases, Vit. K alone will suffice.

5. *Haemorrhage as a result of thrombocytopaenia:* Occasionally anaemia may result from bleeding as a result of a thrombocytopaenia which may be primary or secondary to sepsis, etc. Wherever else bleeding may occur, almost invariably bleeding is manifest in the skin in the form of petechiae or purpura. Besides blood transfusion and corticosteroids, treatment will have to be directed towards the primary cause.

B. Haemolytic Anaemia

The haemolytic anaemias encountered in the newborn are distinctive in that anaemia is accompanied by jaundice which is severe so that in almost every case the infant presents more with a problem in hyperbilirubinaemia and potential kernicterus rather than with anaemia. This is due to the relative immaturity of the liver in this period of life with failure of conjugation of the bilirubin derived from the haemolysed red cells.

The 3 commonest causes in this group include:-

1. ABO incompatibility
2. Rh incompatibility
3. Glucose—6—phosphate deficiency.

In addition to the anaemia and hyperbilirubinaemia, there are the usual haematological signs of compensatory haemopoiesis seen in haemolysis such as a reticulocytosis, normoblastaemia and a hyperplastic normoblastic marrow.

1. *ABO incompatibility:* In this disease, the mother is usually Group O, and the infant Group A or B. Jaundice and anaemia are evident in the first day of life and this is so consistent that such infants can almost be confidently diagnosed as ABO incompatibility in this country. The spleen may be palpable and the blood film may show the presence of microspherocytes. The maternal serum may show haemolytic antibodies to the infant's cells to a high titre.

The degree of anaemia presented by a group of 55 patients studied in the Department of Paediatrics is depicted in Fig. 4.

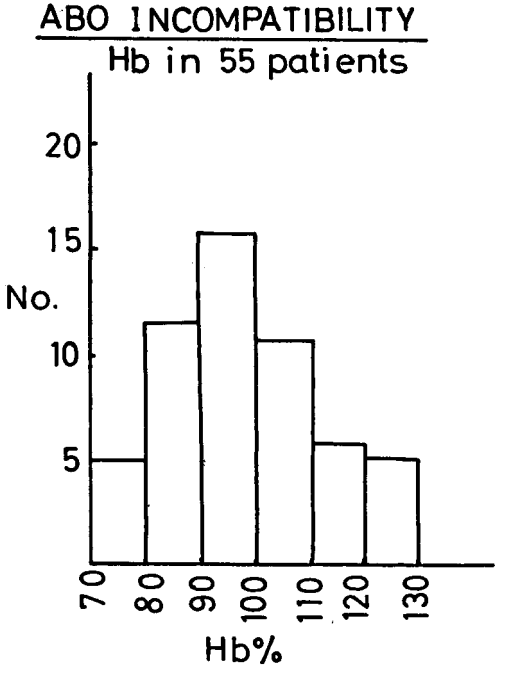

FIG. 4. Showing the degree of anaemia manifested by 55 patients with ABO incompatibility.

The levels of serum bilirubin reached by this same series of patients with ABO incompatibility when they were referred to the Department is depicted in Fig. 5. The number of patients who had high levels of bilirubin illustrates the fact that the main danger is one of hyperbilirubinaemia rather than anaemia.

In the management therefore most of these infants have to be exchange transfused with a topping-up of the anaemia rather than a straight transfusion.

2. *Rh incompatibility:* Rh isoimmunisation is much rarer than ABO incompatibility in Singapore because of the low incidence of Rh negative mothers in the local population. To give an idea of the size of the problem the following figures from 15 live-born cases of Rh incompatiblity

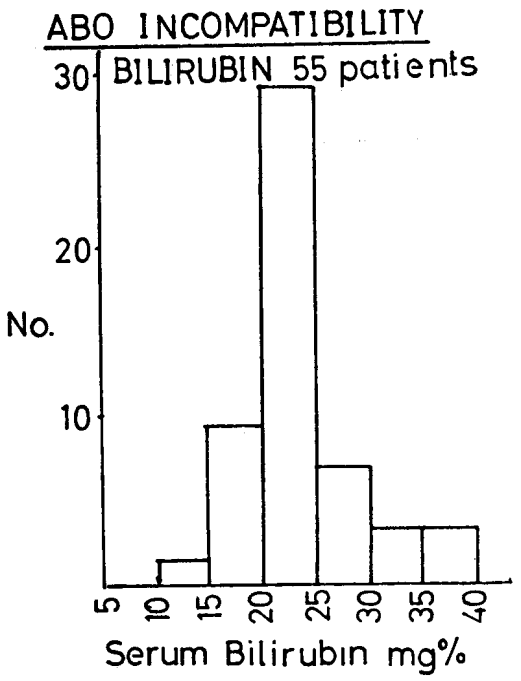

FIG. 5. The intensity of jaundice shown by 55 patients with ABO incompatibility.

encountered in the Department in the last 3 years are illuminating.

Race	No.	
	Alive	Died
Indians	6	1
Chinese	4	0
Europeans	2	1
Eurasians	2	0
Malays	0	0
Total:	14	2

In contradistinction to ABO incompatibility, the problem is not so much the hyperbilirubinaemia as the anaemia. This is due to 2 reasons—firstly, in most instances the involved infant has been anticipated, i.e. the mother is already known to be Rh negative, and hence the infant is seen and assessed immediately after birth so that hyperbilirubinaemia has not occurred, and secondly, in Rh disease the haemolysis is of a greater degree than in ABO incompatibility so that even though Rh babies were seen at birth while ABO babies often seen and assessed on or after the 3rd day of life, the haemoglobin concentration is lower already. Figs. 6 and 7 depict the level of Hb and serum bilirubin at birth.

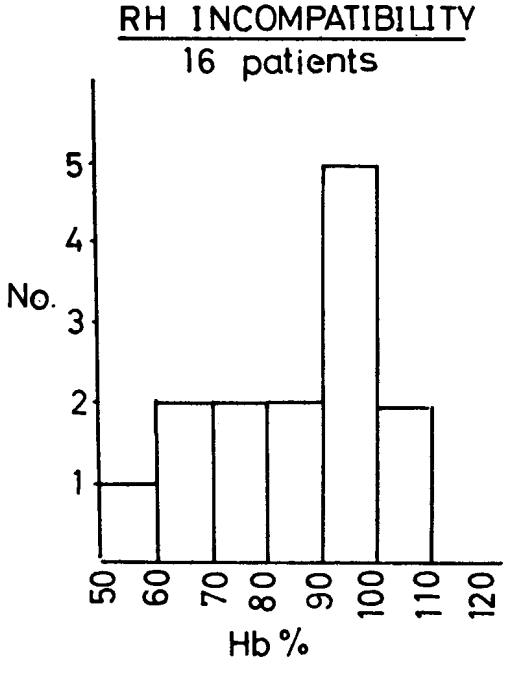

FIG. 6. Showing degree of anaemia presented by 16 patients with Rh incompatibility.

Although Rh disease is less common than ABO disease in Singapore, yet such a patient presents much more problems in management than ABO incompatibility. The haemolysis is more severe, it occurs at a rapid rate in utero so that intrauterine deaths are common, the disease increases in severity in each subsequent pregnancy, and because of the severity, exchange transfusion is a much more hazardous procedure than in ABO disease. It is, however, with the foetus who may die in utero that poses the greatest problem, in other words, when labour should be induced so that a viable baby albeit premature of a stillborn hydrops should result. Yet if labour is induced too early, then the chances of survival as a small premature would

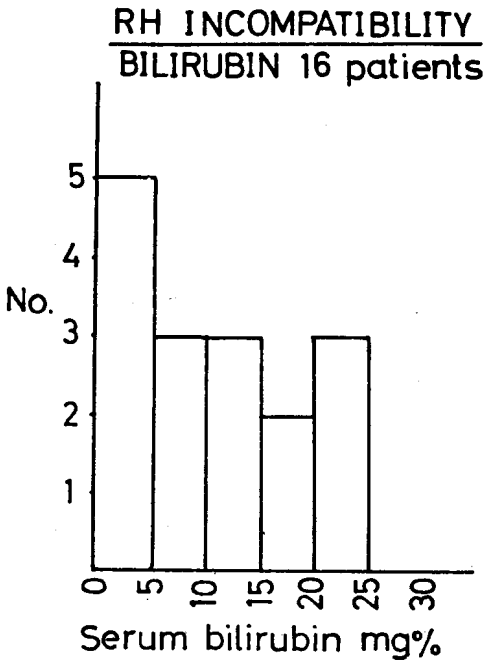

FIG. 7. The degree of jaundice shown by 16 patients with Rh incompatibility on presentation.

be very slim. The problem boils down to a method of assessment of the degree of haemolysis occurring when the foetus is in utero. The time-honoured method of estimating the antibody titre in the mother's serum at different periods of gestation and to induce labour when there is a rapid rise of titre has been found not to be infallible. The estimation of the rise in optical density of the amniotic fluid obtained at amniotomy at 450 mμ and determining where this point will lie in relation to the gestation period will give a very accurate picture of degree of involvement of the foetus.

3. *Glucose-6-phosphate deficiency:* The role of G6pd in the causation of neonatal hyperbilirubinaemia in Singapore has been fully documented (Wong), and since the hyperbilirubinaemia is due to a combination of haemolysis an liver immaturity, such infants seldome present as a problem in anaemia. In fact, the average Hb of a large series of G6pd deficient infants with hyperbilirubinaemia (Wong, 1965) was found to be around 15 Gm% on the 4th or 5th day of life. In a series of G6pd deficient infants and G6pd normal infants (Brown & Wong, 1965), the cord haematocrit and Hb were only slightly lower in the enzyme deficient infants compared to normals as can be seen in the following table:-

	Haematocrit %	**Haemoglobin** %
G6pd deficiency	45·7 ± 4·9	98·7 ± 10·7
G6pd normal	50·8 ± 6·6	105 ± 9·7

Very rarely, the haemolysis may be severe enough to result in significant anaemia.

The anaemia in G6pd deficient infants is due to the effect of exogenous drugs on such cells and the common drugs found to trigger off haemolysis in this country include the many native herbal medicines taken by mothers breast feeding their infants and also directly given to newborn infants, phenacetin, sulphanamides, excessive doses of Vit. K. Examination of the blood incubated with methyl violet would reveal multiple fine intraerythrocytic bodies called Heinz bodies, and in fact, G6pd deficiency haemolytic anaemia is one variety of Heinz body anaemia.

It is often asked whether the congenital inherited forms of haemolytic anaemia seen in Singapore, viz. the haemoglobinophathies and congenital microspherocytosis ever present in the newborn period as a problem in anaemia. In the case of the haemoglobinopathies, there is no significant anaemia detected at birth or in the neonatal period, and anaemia if severe, only appearing in the 3rd month. As a corollary, such newborns almost never present as a problem in hyperbilirubinaemia either. However, very occasionally, congenital microspherocytosis may present with anaemia and hyperbiliruinbaemia in the newborn period although the majority present with anaemia much later in life. The difficulty of diagnosing congenital microspherocytosis in an infant presenting with anaemia and jaundice in the first week of life is the fact that microspherocytes can also be seen in ABO incompatibility which is much more common. So far, we have only encountered

one patient with congenital microspherocytosis whose anaemia and jaundice appeared in the first week of life and he had to have an exchange transfusion, and in fact kernicterus has been described in such infants. Therefore, as a general rule, the congenital inheritable forms of haemolytic anaemia do not present with anaemia in the newborn infant.

However, there is one notable exception to the foregoing generalisation and that is a haemoglobinopathy affecting Chinese infants, viz. hydrops foetalis due to Bart's Hb—an ∝-thalassaemia. But for practical purposes from the point of view of management it is at present of no consequence as these infants are stillborn or if liveborn have all died within a few hours after delivery.

C. Anaemia of Prematurity

If there is no bleeding, all premature infants are not anaemic at birth, but because of the rapid rate of growth and greater dormancy of the marrow compared to full-term infants the fall in Hb in early infancy and the behaviour later on are exaggerated. The shorter life-span of their erythrocytes may also contribute to the anaemia. Because of all these reasons there are 2 periods when anaemia may occur:-

a) The *early anaemias of prematurity* which occurs at about 2 months of age—this anaemia is inevitable and is normochronic in type.

b) After this period the Hb rises a little as the bone marrow is stimulated and depending on the stores of iron which may be available for the rapid increase in growth, the Hb may be maintained or it may fall. If at this stage, the iron stores are inadequate to provide for the rapid expansion of the vascular space then anaemia may set in again. This is the *late anaemia of prematurity* and is an iron deficiency type, i.e. it is hypochromic.

Fig. 8 is constructed from Hb figures obtained in the prospective follow-up of 39 premature infants from K. K. Hospital from birth to 1 year. The Hb curve has been constructed by calculating the mean Hb levels at different ages. The early anaemia of prematurity is noted at

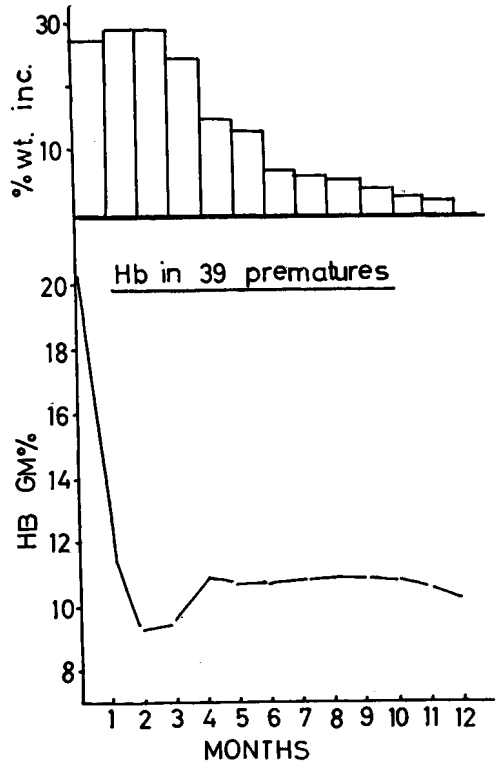

FIG. 8. Mean Hb levels in 39 prematures showing the low level reached at 2 months (early anaemia) due to rapid weight increase gradient.

about 2 months when it reaches 9 Gm% — i.e. the late anaemia of prematurity. All the 39 datients were given oral iron preparations from the age of 2 weeks but whether they were given the medication after discharge by the mothers is problematical.

In the same figure, the mean rate of increase in weights of the 39 prematures at different ages are drawn and the rapid fall in Hb in the first 2 months becomes very evident as it is during this period of life that the weight increase gradient is maximal.

D. Aplastic Anaemia

Aplastic anaemia either congenital or acquired are extremely rare in infancy and manifestation early after birth is even rarer still. The congenital variety can be seen in 2 affections, viz.

a. Erythrogenesis imperfecta, where there is aplasia of the red precursors only with-

out involvement of the white and the megakaryocytes. Anaemia usually is manifested about 3 months of age.

b. Fanconi's anaemia where there is aplasia of all 3 elements often associated with other congenital anomalies such as polydactyly, microcephaly, microphthalmia etc.

Aplastic anaemis almost never presents as a problem in anaemia at birth.

Incidence

The incidence of the various causes of anaemia in this country at birth or within the first week of life can be gauged by the following figures obtained in K. K. Hospital in 1962 and 1963 of only full-term babies. It must be emphasized that this is not necessarily the absolute figures for Singapore since they have been obtained from a partially selected group, and furthermore, the degree of anaemia varies in the different patients depending on the severity of the condition. However, in all cases anaemia had either been a problem or could have been a problem later on with growth of the infant.

Full-term infants KKH (1962-1963)

Haemorrhage:

Cephalhaematoma	209
Haematoma of cord	73
Intracranial haemorrhage	72
Bleeding from cord	47
"Haemorrhagic" disease of newborn	47
Twin anaemia	11
Scalp haemorrhage	5
Adrenal haemorrhage	4
Liver haemorrhage	1
ITP	2

Haemolytic:

ABO incompatibility	36
Rh incompatibility	9

References

Brown, W.R. & Wong, H.B. (1965). To be published.

Chalmers, D.G., Smith, A.J. & Worssam, A.R.H. (1957). Guy's Hosp. Rep. 106, 65.

Gairdner, D., Marks, J., Roscoe, J.D. (1952). Arch. Dis. Childh. 27, 214.

Gairdner, D. (1958). Recent Adv. in Paediat. Ed. Gairdner, D.J. & A. Churchill Ltd., London.

Guest, G.M., & Brown, E.W. (1957). Amer. J. Dis. Child., 43, 486.

Mackay, R.B. (1957). J. Obstet. Gynaec. Brit. Emp. 64, 185.

Marks, J., Gairdner, D., & Roscoe, J.D. (1955). Arch. Dis. Childh. 30, 117.

Rooth, G., & Sjostedt, S. (1957). Arch. Dis. Childh. 32, 91.

Sturgeon, P.S. (1956). Pediat. 18, 267.

Wong, H.B. (1965). J. of Singapore Paed. Society, (in the press).

Wong, H.B. (1965). Unpublished observations.

Zipursky, A.; Hull, A; White, F.D. & Israels, L.G. (1959) Lavet, 1, 451.