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H Bard, J Prosmanne

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Research Article

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Postnatal Fetal and Adult Hemoglobin Synthesis in Preterm Infants Whose Birth Weight Was Less Than 1,000 Grams

HARRY BARD AND JANIE PROSMANNE, *Perinatal Service and Centre de Recherche Pédiatrique of St. Justine's Hospital, Department of Pediatrics, University of Montreal, Quebec, Canada*

ABSTRACT To determine if environmental factors could effect the switchover from fetal hemoglobin (HbF) to adult hemoglobin (HbA) synthesis, studies were carried out on blood samples from eight infants born at <1,000 g, when they had reached their postconceptional age corresponding to term. All of these infants required prolonged intensive care, multiple blood transfusions, and two required exchange transfusions. Several were ventilated mechanically for 60 d and two infants had bronchopulmonary dysplasia at the time of the study. The blood samples were incubated in an amino acid mixture containing [¹⁴C]leucine followed by column chromatography on DEAE Sephadex for separation of radioactive HbA and HbF. In spite of the extreme prematurity and poor growth of these sick infants, the proportional synthesis of HbF and HbA, as determined by the incorporation of [¹⁴C]leucine during the erythrocyte incubations, was characteristic of the period of human development from which the erythrocytes were obtained.

INTRODUCTION

Recent developments in clonal cell culture methods for early erythropoietin precursors have made it possible to study hemoglobin synthesis in culture in relation to the stages of maturation of the human erythrocyte precursors (1, 2). Based on these studies it has been suggested that the regulation of fetal hemoglobin (HbF)¹ is inversely related to the degree of differentiation of the human erythroid cells known as burst-forming units. Also from these studies it has been suggested that the switch from HbF to adult hemoglobin (HbA) as development proceeds can be explained by the derivation of erythrocytes from progressively more differentiated burst-forming units and the reappearance of HbF under pathological conditions by the

recruitment of erythrocytes from less differentiated burst-forming units.

Since the perinatal period is the time of active switchover from HbF to HbA synthesis in humans and can provide an in vitro representation of hemoglobin type synthesis in peripheral blood during early human development, a study was planned to determine if environmental factors could have any effects on the switchover from HbF to HbA synthesis. This was to be done by evaluating Hb synthesis in a group of very early preterm newborn infants born at <1,000 g who were sick and required prolonged intensive care. The data obtained from these infants would be compared with that previously published and any differences could then be correlated with the pathology or therapy.

METHODS

Eight early preterm infants appropriate in weight for gestational age with no evidence of congenital anomalies were selected for the study. They were carefully chosen at birth on the basis of a close correlation between the clinical estimate of gestational age, based on the one hand on external characteristics and neurological status, and on the other hand, on the menstrual history estimate. Their correlated gestational ages at birth ranged from 26 to 30 wk. Also included as term controls were four full-term infants who were appropriate in weight for gestational age (3).

The proportional synthesis of HbF and HbA was determined by measuring the incorporation of [¹⁴C]leucine into the hemoglobins formed during the in vitro incubation of reticulocytes by methods previously described (4). The radioactive hemoglobins were prepared from samples obtained for analysis from the preterm infants when they reached the postconceptional age equivalent to term. The data for the full-term infants appropriate in weight for gestational age were obtained using placental cord blood collected immediately after birth. The distribution of the birth weights and gestational ages of the infants studied is shown in Fig. 1.

RESULTS

The infants of the study all received some adult blood either as packed cells, whole blood or by exchange

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¹Abbreviations used in this paper: HbA, adult hemoglobin; HbF, fetal hemoglobin.

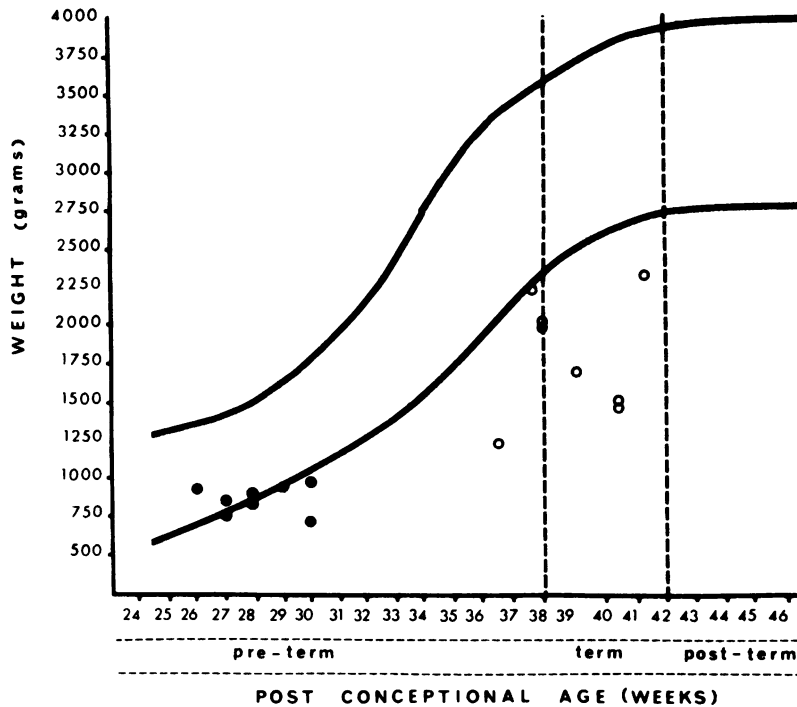


FIGURE 1 The distribution of the infants < 1,000 g at birth (●) and on the day of sampling (○), on the Colorado intrauterine growth chart (3). Solid lines represent the 90th and 10th percentiles.

transfusions (for treating hyperbilirubinemia). They were all initially nourished by intravenous hyperalimentation, and were all growth retarded according to the intrauterine growth charts at the time of analyses. Two of the infants required assisted ventilation for more than 2 mo and two had broncho-pulmonary dysplasia (5) when sampled. (These data are summarized in Table I.)

A representative hemoglobin elution is shown on Fig. 2. This infant required two exchange transfusions (at 2 and 3 d of age) because of hyperbilirubinemia.

The infant's blood contained 28.9% HbF and 71.1% HbA. However, the synthesis was 57.4% HbF and 42.6% HbA. This was the expected proportions at 40.5 wk postconceptional age.

The comparison of the data on HbA and HbF synthesis to what has been published previously (6) is shown on Fig. 3. This figure illustrates that these very low birth weight infants who required prolonged intensive care have synthesis HbA and HbF in normal expected proportions when evaluated at the postconceptional age corresponding to term.

TABLE I
Therapy and Morbidity of the Infants < 1,000 Grams at Birth

Weight of infants at birth	Number of transfusions packed cells (or whole blood) 10-20 cm ³	Number of exchange transfusions	Parenteral nutrition	Assisted ventilation	Broncho-pulmonary dysplasia	Weight day of sample
g			d	d		g
900	2		14	1		1,980
860	2		14	2		2,230
980	3 (1)	2	9			1,220
730	6 (1)	2	2			1,470
820	15 (1)		38	10	Yes	2,320
755	18 (8)		55	60		1,700
945	3 (1)		1	1		2,000
945	19 (1)		54	62	Yes	1,500

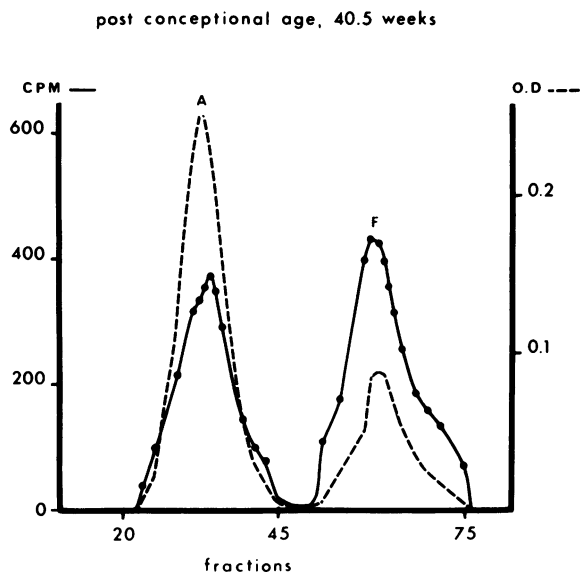


FIGURE 2 The postnatal A and F hemoglobin synthesis in an infant born at 30 wk of gestation at < 1,000 g required two exchange transfusions, studied at 40.5 wk postconceptional age. The superimposed tracings represent the Sephadex-DEAE chromatographic separation of adult and fetal hemoglobin absorbance 280 nm (---) and counts per minute of [¹⁴C]leucine labeled hemoglobins (●-●-●). Total fetal hemoglobin 28.9%, radioactive fetal hemoglobin 57.4%.

DISCUSSION

This study aimed to answer the question whether sick infants <1,000 g who were born prematurely and exposed to numerous stresses would have an altered pattern of fetal and adult hemoglobin synthesis. Previously it had been shown that preterm infants born at

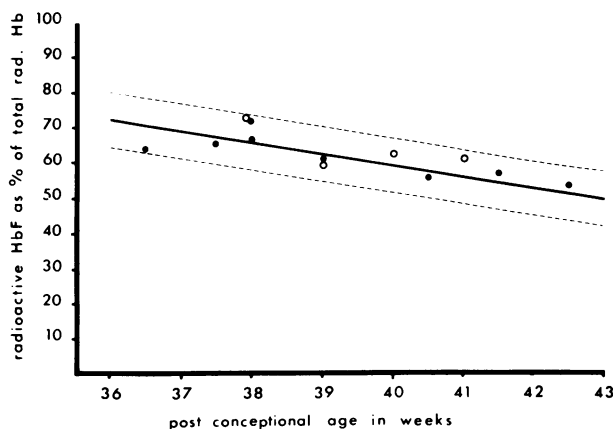


FIGURE 3 Radioactive fetal hemoglobin as a percentage of the total hemoglobin in relation to postconceptional age. ● are the infants < 1,000 g, ○ are the control term newborn infants, (—) the mean and (---) 95% confidence limits from a previous study reflecting *in utero* A and F hemoglobin synthesis (1).

<32 wk of gestation had a rate of transition from HbF to HbA synthesis postnatally that is similar to the fetal switchover in utero (4). That earlier study was completed 10 yr ago when the neonatal intensive care unit had very few survivors at <28 wk of gestation and those that did survive were the infants that had minor or no neonatal complications. Thus, most of the data obtained at the end of that previous study were from normal infants that survived and were born near 32 wk of gestation.

At the present time the incidence of survival rate of preterm newborn infants <1,000 g is near 50%. However, these infants require a prolonged period of intensive care and often have the complications of pulmonary disease treated with assisted ventilation. They also need numerous blood transfusions as well as exchange transfusions and are initially nourished by total parenteral nutrition (intravenous amino acid and lipids). They are in many cases oxygen dependent for long periods of time and grow at a slower rate than the accepted intrauterine growth pattern (3).

The transition from HbF to HbA synthesis on the human fetus is precisely timed and coordinated during intrauterine life. The data from the present study indicate that the very immature sick preterm infant who survived the neonatal period, had erythroid cells that were producing the proportions of HbF and HbA that was characteristic of their postconceptional age. Therefore a very precocious and stressful exposure to the extrauterine environment does not effect the timing of the switchover from HbF to HbA synthesis.

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