# HYPERVISCOSITY IN THE NEWBORN INFANT

## A CLINICAL STUDY

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## DECLARATION

I, Clive Willem van der Elst, hereby declare that this thesis is my own work and has not been presented for any degree at another university.

Signed Signed by candidate Date 9th March 1987

The work reported in this thesis was performed in the Department of Paediatrics and Child Health, University of Cape Town, Cape Town.

## DEDICATION

To Libby, Colin and Lise,
whose patience and
understanding made the
writing of this thesis possible.

And to the patients without
whom this work could not have
been done.

ABSTRACT

This study focuses on neonatal polycythaemia with associated hyperviscosity (NPHV). It examines the controversial issue of treatment with partial plasma exchange transfusion (PPET) in newborn babies who do not have any signs or who have only minor clinical signs of NPHV. The aim of this work is to compare the effect of treating or not treating this condition by assessing the children from birth until 7 years of age. A long term study of this nature had not been done previously.

Before the above aim could be addressed, it was necessary to direct attention to methods of blood sampling for the haematocrit (Hct) determination and to normal Hct and blood viscosity values for the local population.

Polycythaemia in the newborn (Hct $\geqslant$ 65%) is best diagnosed with blood from a central vessel. In this study, blood from the cubital vein was used and was considered to represent a central sample. It was found that blood taken for Hct from an unwarmed heel gave falsely high results (mean 9,7 $\pm$ 12%), while warming the heel improved the relationship (mean 2,0 $\pm$ 8,6%) when these values were compared with a central venous sample. The incidence of babies being hyperviscous when the warmed heel prick Hct was $\geqslant$ 65% was 68%; yet when central venous blood was sampled and the Hct was $\geqslant$ 65%, the incidence was 91%.

A small sample (n = 10) of normal babies was examined from birth until 4 days of life to determine whether their Hct and viscosity levels were similar to those in the published literature. It was found that the central venous Hct ranged from a mean of 46,2 $\pm$ 12,1% (cord blood)

through 52,2 $\pm$ 12,2% at 12 hours of age, and to 47,1 $\pm$ 8,2% by day 4. Blood viscosity (e.g. at shear rate 11,5 $sec^{-1}$) was also low, 7,72 $\pm$ 3,3 $sec^{-1}$, in cord blood and rose to 9,73 $\pm$ 4,96 $sec^{-1}$ at 12 hours of age. By day 4, the value was 9,91 $\pm$ 2,7 $sec^{-1}$. Local cord blood values for Hct and viscosity were similar to those published by Gross et al (1973) and Mackintosh and Walker (1973) for the first day of life.

Having established these two stated objectives, the aim of the study could then be examined. At the outset 41 babies with NPHV and no apparent or only MINOR clinical signs were identified. They were randomly assigned to two groups, Group A and Group B.

Group A babies (n = 20) had a mean central Hct of 70 $\pm$ 4,5% and viscosity of 18,3 $\pm$ 3,1 cps at 11,5 $sec^{-1}$. These babies received a partial plasma exchange transfusion.

Group B babies (n = 21) had a mean central Hct of 68,1 $\pm$ 3% and viscosity of 17,18 $\pm$ 2,8 cps at 11,5 $sec^{-1}$. These babies were not exchanged.

A further group, Group C (n = 31), of matched controls, (central Hct 48,9 $\pm$ 4,7% viscosity 8,7 $\pm$ 1,9 cps at 11,5 $sec^{-1}$) was included for comparison.

There were no significant differences between the groups when anthropometric measurements, the sex of the infant and the Apgar Score were compared. The chest radiograph, electrocardiogram and plasma magnesium determinations were similar when the 2 hyperviscous groups were compared. The major difference between the groups was in the Hct and blood viscosity levels. Group A had been polycythaemic and

hyperviscous at birth and had been treated by PPET. Group B babies were polycythaemic and hyperviscous at birth but were not treated with PPET. Group C had a normal Hct and blood viscosity.

Findings during the neonatal period were that NPHV babies were frequently small for gestational age (11 in Groups A and B), had radiological signs of pulmonary plethora (17 out of 41) and alveolar infiltrates (6 out of 41). The plasma calcium levels, although normal, were significantly lower than those of the control group, Group C. Clinical signs, particularly signs of gastrointestinal origin including necrotizing enterocolitis, were more frequent in NPHV babies (6 out of 41). Neonatal behavioural testing showed that babies with NPHV had problems interacting with the examiner.

Examination of the children in Groups A and B, when they were 6-7 years of age, showed significant differences when compared with the controls. Neurological scores (Group A vs C - $p = 0,016$, Group B vs C - $p = 0,003$), non-verbal intelligence (Group B vs C - $p = 0,031$) and visual perceptual scores (Group A vs C - $p = 0,04$, Group B vs C - $p = 0,022$) were all lower than controls but were nevertheless within the range of normal values. Treatment with PPET did not improve the outcome of the NPHV babies in any statistically significant way.

It is proposed from the results of this study that the causes of NPHV, rather than the NPHV itself, could result in sequelae. The complications observed in babies with NPHV are more likely to be due to the condition that caused the NPHV than the hyperviscous state itself. It is further proposed that newborn babies with NPHV who have no apparent or only minor signs do not benefit from treatment with PPET either in the neonatal period or in later life.

PUBLICATIONS

The following articles, related to this thesis, were published in refereed journals.

1. van der Elst CW, Malan AF, Heese HdeV. Blood viscosity in modern medicine. S Afr Med J 1977; 52:526-528.

2. van der Elst CW, Malan AF, Heese HdeV. Haematocrit values and blood viscosity in the normal infant. S Afr Med J 1978; 53:494-496.

3. van der Elst CW, Malan AF, Heese HdeV. Blood viscosity in the normal newborn baby. S Afr Med J 1978; 53:538-540.

4. van der Elst CW, Malan AF, Heese HdeV. Blood viscosity during fluid infusion in the preterm infant. S Afr Med J 1979; 55:211-212.

5. van der Elst CW, Molteno CD, Malan AF, Heese HdeV. The management of polycythaemia in the newborn infant. Early Hum Dev 1980; 4:393-403.

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## SYMBOLS AND ABBREVIATIONS

| | | |
|---|---|---|
| ANOVA | = | Analysis of Variance |
| AGA | = | Appropriate for gestational age |
| C | = | Gap width |
| cps | = | Centepoise |
| CBF | = | Cerebral blood flow |
| CNS | = | Central Nervous System |
| Group C | = | Control group |
| $\geqslant$ | = | Equal to or greater than ... |
| $\leqslant$ | = | Equal to or less than ... |
| GIT | = | Gastrointestinal tract |
| $>$ | = | Greater than ... |
| Hct | = | Haematocrit |
| HV | = | Hyperviscosity |
| Group A | = | Hyperviscous exchanged group |
| Group B | = | Hyperviscous, not exchanged group |
| IQ | = | Intelligence Quotient |
| LGA | = | Large for gestational age |
| L | = | Length |
| $<$ | = | Less than ... |
| NCHS | = | National Centre for Health Statistics |
| NEC | = | Necrotizing enterocolitis |
| NBAS | = | Neonatal Behavioural Assessment Scale |
| NP | = | Neonatal polycythaemia |
| NPHV | = | Neonatal polycythaemia associated hyperviscosity |
| NSAIS | = | New South African Individual Scale |
| O | = | Cone angle |
| PPET | = | Partial plasma exchange transfusion |
| $\Delta P$ | = | Pressure gradient |
| R | = | Resistance |
| r | = | Cone radius |
| SGA | = | Small for gestational age |
| T | = | Torque |
| $\mu$ | = | Viscosity |
| V | = | Volume flow |
| W | = | Constant Speed |

## DEFINITIONS

| | |
|---|---|
| Dynamics | The science of motion and forces. |
| Rheology | The study of the deformation and flow of matter. |
| Viscosity | Ratio of shear stress to shear rate. |
| Haematocrit | A capillary tube (1,1 x 75 mm) determination of the volume of erythrocytes in centrifuged whole blood expressed as corpuscular volume percent. The term haematocrit is preferred to that of packed cell volume. |
| Plethora | The appearance of vascular turgescence due to an excess of red blood corpuscles. |
| Polycythaemia | A central venous haematocrit value equal to or greater than 65 percent. |
| Term | Gestational age from the beginning of the 37th week to the end of the 42nd week. |
| Preterm | Gestational age less than 36 completed weeks. |
| Post term | Gestational age more than 42 completed weeks. |
| Small-for-Gestational Age | Birth weight less than the 10th Percentile (NCHS). |
| Large-for-Gestational Age | Birth weight more than the 90th Percentile (NCHS). |
| Appropriate-for-Gestational Age | Birth weight equal to or between the 10th and 90th percentiles (NCHS). |
| Sensitivity | If the disease is present, is the test positive ? |
| Specificity | If the disease is absent, is the test negative ? |
| Postive predictive Accuracy | If the test is positive, how likely is the disease to be present ? |
| Negative predictive Accuracy | If the test is negative, how likely is the disease to be absent ? |

| | |
|---|---|
| Shear stress | The force (dynes/cm$^2$) required to move different fluid laminae. |
| Shear rate | The difference in velocity ($sec^{-1}$) of 2 fluid laminae divided by the distance between them. |

# PREFACE

## INTRODUCTION, AIM AND OBJECTIVES

The management of the newborn infant with neonatal polycythaemia and hyperviscosity (NPHV) of the blood is a controversial subject (Oski and Naiman 1982, Hathaway 1983). The condition of hyperviscosity may be associated with life-threatening complications (Gross et al 1973), with insults occurring mainly in the central nervous, the cardiovascular, respiratory, renal and intestinal systems. There is therefore consensus amongst most paediatric physicians that hyperviscous infants with serious side effects should be treated and that the preferred method of therapy for these babies is a partial plasma exchange transfusion (PPET). This form of therapy has been shown to be of clinical benefit to affected babies (Woods 1959, Kontros 1972).

However, many babies are born with NPHV and do not manifest serious complications. In fact, it would appear that the majority of babies are asymptomatic and that if signs do appear these are of a minor nature (Høst and Ulrich 1982). The incidence of NP is variously reported to be between 1,14% and 12% and consequently if all babies with NPHV require treatment, as has been suggested (Black et al 1982(b), then considerable numbers of exchange transfusions would be necessary. An additional consideration is that the method of treatment with PPET is itself associated with complications including the risk of necrotizing enterocolitis (Black 1985(b)).

Neonatal polycythaemia with hyperviscosity is also associated with central nervous system damage and this might only manifest itself in later years (Goldberg et al 1982, Black et al 1982(a)). It has therefore been proposed by some authorities that early treatment of NPHV babies with PPET could prevent later sequelae. This has not been found to be true, and it is still not clear whether the NPHV itself or its cause is responsible for the CNS dysfunction seen in these babies. Nor is it clear that the treatment given will necessarily improve the outcome of these children. Polycythaemia with resultant hyperviscosity is thought, in some instances, to be a consequence of tissue hypoxia and the CNS damage that occurs may be a direct result of this insult. Alternatively, the baby may have become polycythaemic and hence hyperviscous because of other adverse intrauterine conditions. These conditions themselves may have resulted in CNS compromise. Theoretically, treatment with PPET could improve the outcome in babies affected by the hyperviscous state per se, while there would be little or no benefit to those NPHV babies who were damaged by other causes.

In 1976, when work for this present study began, only one paper (Goldberg et al 1976) reported on the outcome of treatment with PPET of NPHV babies. The study examined 22 hyperviscous babies randomised to receive treatment with PPET or not be exchanged. These 22 infants plus 10 control babies with normal blood viscosity were followed for 8 months. Although untreated NPHV was associated with an increased incidence of neurologic abnormalities, the therapeutic benefit of PPET could not be demonstrated. Yet despite these findings the general recommendation for all cases of NPHV remained PPET. It was also clear at this time that there were no studies that had examined the long term outcome (i.e. 7 years) of NPHV and the effect of treatment. The

findings at 8 months did not necessarily predict how these children would perform when they were older. It was important that in order to advise whether treatment with PPET was beneficial or not, that a long term outcome study needed to be done.

It was this consideration which prompted the idea that a study should be done in which relatively asymptomatic NPHV babies would be randomly assigned to receive PPET or not be exchanged. The outcome both in the neonatal period and subsequently at 6-7 years of age would be compared with a matched non-hyperviscous control group.

Two further problems were considered before the main study was addressed. Firstly, it had been noted that in the newborn there were considerable variations in Hct and viscosity values when blood samples were taken from different sites. Peripheral samples (e.g. from heelprick blood) tended to give high results while central venous samples, from the same infant, gave remarkably lower values. Clarity regarding the method of sampling was needed.

Secondly, it was necessary to establish whether normal babies in the local community had similar Hct and blood viscosity levels to those levels published in the international literature. A review of published Hct and blood viscosity levels showed that there were marked differences in normal reference values given by the various authors. Therefore, it was necessary to establish norms for babies in the local population.

In summary therefore:

## OBJECTIVES

1. Method of Sampling:

   Determine the effects of different methods of peripheral capillary and venous blood sampling on haematocrit values and their relationship with whole venous blood viscosity.

2. Normal Viscosity Values

   Determine whether a group of normal babies from the local population had similar blood haematocrit and viscosity levels to those published in the literature.

## THE AIM

### The Hyperviscosity Treatment Study

The aim of this long term study is to determine whether treatment with partial plasma exchange transfusion would prevent the occurrence of short or long term sequelae in NPHV babies who have minor or no clinical signs at birth. This study examined the question in these children longitudinally from birth until 6-7 years of age.

## NULL HYPOTHESIS

The null hypothesis for this study states that there will be no difference in the outcome of hyperviscous newborns with no apparent or only minor clinical signs, whether treated or not treated with partial plasma exchange transfusion.

# PART I

# REVIEW

## CHAPTER 1 : HAEMODYNAMICS

### 1.1 INTRODUCTION

Neonatal polycythaemia and the resultant hyperviscosity are known to alter blood flow in babies. To better understand these changes it is necessary to review, in some detail, the physical concepts that relate to the movement of blood in the cardiovascular system (Brobeck 1980). The term dynamics refers to the science of motion and forces as applied to matter, while the term haemodynamics is the study of the movement of the blood.

The cardiovascular system distributes blood to, and collects blood from diffusion sites in the body. To achieve this a complex system of pressure and flow properties exists which are governed by and responds to various metabolic requirements and functional inter-relationships in the body. The heart, which functions as 2 pumps in series must, of necessity, deliver the same fluid volume output under all normal circumstances. The distribution of blood within the circulation and perfusion depends largely on volume flow, pressure and resistance. In discussing each of these factors it must be appreciated that the cardiovascular system is not a uniform or 'ideal' system of tubes but instead a complex maze of branching vessels of

different sizes and shapes, able to contract and dilate, subject to temperature variations and with irregular inner wall surfaces. In addition, vessel wall anatomy, distensibility and vasomotor properties all influence the movement of blood within the system. Some approximation of events in the system can however be made and this gives us some insight into the laws governing haemodynamics.

## 1.2 VOLUME, PRESSURE AND RESISTANCE

The mechanical relationships between volume, pressure and resistance in their simplest form are expressed as:

$$\text{Volume (V)} = \frac{\text{Pressure (P)}}{\text{Resistance (R)}}$$

Haemodynamically, volume (V) refers to blood flow volume (ml/sec), pressure (P) to the pressure gradient ($P_1 - P_2$) (mmHg or cm $H_2O$) across the vessel length and resistance (R) (dyne sec/cm) to the geometry of the tubular system and the viscosity of the fluid.

## 1.3 RESISTANCE

The above formula can be expressed algebraically as:

$$R = \frac{P}{V}$$

such that resistance directly determines pressure. Thus, where R is high the pressure gradient drop will be large and the volume of flow is smaller.

If it is assumed that the viscosity of the blood is constant, the factors determining resistance are the lengths of the conduits, their cross sectional area and whether they are arranged in parallel or in series. Resistance is directly proportional to conduit length (R x L) so that the longer the vessel and the further the blood must slip to reach its destination the greater will be the total friction or resistance. Resistance also increases inversely with the cross sectional area of the vessel. ($R = 1/PI\ r^2$). A narrow vessel will deliver less fluid than a wide one when the pressure and length are kept constant. The configuration of the vessels within the system will also have an effect on resistance. Thus the total resistance of a number of vessels arranged in series is the sum of each vessel's resistance ($R\ total = R_1 + R_2 + R_3$ etc) while the total resistance of vessels in parallel is the sum of the reciprocal of the conductance of each vessel:

$$R\ total = \frac{1}{\frac{1}{R} + \frac{1}{R} + \frac{1}{R}} \text{ etc}$$

In the human body each of these factors varies with physiological demands so that the calculation of resistance at any one point or time is extremely complex. Additional factors including the effects of autoregulation, hormones, nerve impulses and vasoactive substances also need to be considered. Because of this, the application of rigid laws to determine the haemodynamic status of the cardiovascular system in man must of necessity be an approximation.

## 1.4 BLOOD FLOW

Other factors beside the pressure gradient and the volume will affect the flow of blood in the circulation. These factors alter the resistance to fluid (blood) flow and have a major influence on tissue perfusion.

The flow of a fluid through a uniform tube under a constant pressure is found to be linear when the fluid elements are homogeneous in nature. Thus, if a bolus of dye (particles of uniform size) is injected into a liquid (e.g. water) flowing in a glass tube the leading edge of the dye appears as a travelling parabola. This streamlining of the flowing dye indicates that the cylinder of moving fluid is made up of concentric laminae sliding over one another. The fluid molecules nearest the walls of the tube will be static whilst those nearest the axis flow fastest. The force required to move these laminae of fluid is referred to as the SHEAR STRESS (dynes/cm$^2$) while the difference in velocity of 2 fluid laminae divided by the distance between them is known as the SHEAR RATE (sec$^{-1}$). The ratio of shear stress to shear rate is the VISCOSITY ($\mu$) of the fluid. The measurement of Viscosity (SI units: centepoise) relates to its thickness, stickiness or the internal forces that resist flow. The resistance to flow of a fluid is directly proportional to the viscosity ($r \propto \mu$) of that fluid. Fluids can be divided into 2 types according to their viscous behaviour. When the viscosity of a fluid remains constant despite changes in the velocity then that fluid will behave in a linear way. These fluids (e.g. water, oils) are known as Newtonian fluids. This means that the viscosity of the fluid will remain constant

despite an increase or decrease in the velocity at which the fluid is made to move.

Some fluids however behave differently in that viscosity changes with change in velocity. These are called non-Newtonian fluids. Blood is an example of a non-Newtonian fluid because the viscosity increases exponentially with a decreasing shear rate. The heterogeneous nature of blood (RBC's, WBC's, platelets, proteins, fats etc) is probably the reason for its non-linear behaviour. (Figure 1.1)

Poiseuille (1846) was the earliest research physician to formulate the dynamics of viscosity. Working with glass capillary tubes and water he was able to relate viscosity ($\mu$) to the radius of the tube (r), its length (L), rate of flow volume (V) and pressure gradient (PI) such that:

$$\mu = \frac{PI \quad r^4}{8 \quad L \quad V}$$

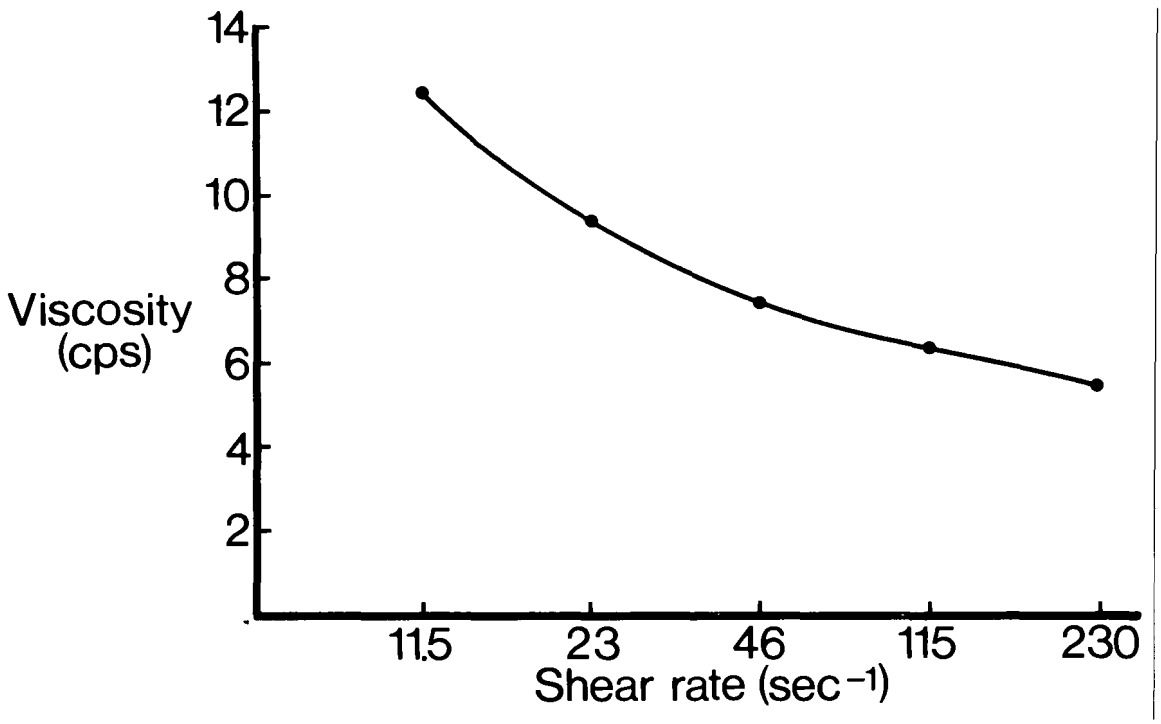
This relationship is fundamental to the understanding of viscosity and is acceptable for Newtonian fluids. Of note is the fact that the radius of a tube has a marked effect on the viscosity so that if it is doubled the viscosity will increase 16 times.

The relationship between viscosity and resistance can be obtained by substituting P/V for R so that :

$$R = \frac{8 \quad L \quad \mu}{PI \quad r^4}$$

FIGURE 1.1

WHOLE BLOOD (Hct 55%) VISCOSITY AT VARYING SHEAR RATES



Conditions within the circulation limit the absolute application of Poiseuille's formula. Firstly, for example, in large arteries and veins (e.g. aorta and vena cava) blood can be considered to behave as a homogeneous fluid with its viscosity being independent of velocity gradient. As the vessel becomes smaller and the flow velocity less the viscosity increases exponentially. This non-Newtonian behaviour is demonstrated in vessels of decreasing size until the vessel diameter becomes extremely small. In these small vessels the influence of the vessel diameter, known as the Fähraeus-Lindquist effect (1931), applies. Here, the apparent viscosity of blood decreases with the increased flow velocity and this also occurs with the reduction in vessel radius. The blood viscosity in vessels $< 0{,}5$ mm and especially $< 0{,}3$ mm falls anomalously. This is because the red cells become concentrated in the axial part of the stream and a cell free plasma zone is formed close to the walls. Branched vessels will receive blood with a lower haematocrit (because of plasma skimming) and hence will have a lower apparent viscosity.

Secondly, blood flow does not occur in a laminar way parallel to the vessel wall throughout the cardiovascular system. Changes in vessel wall direction (bends) and branching characteristics disrupt the streamlined flow and cause a greater resistance than would otherwise be expected. In vessels subject to high flow velocities (e.g. aorta) turbulence occurs. There is a particular point (Reynolds Number 1883) at which laminar flow ceases in these vessels and turbulent flow occurs. This critical point is itself dependent on fluid density and blood viscosity.

Thirdly, the rate of flow within the system is pulsatile and not constant so that Poiseuille's experimental laws of linear flow cannot apply.

A fourth consideration is that blood vessels are not rigid tubes but instead distensable elastic vessels whose diameter varies with pressure and tone. Blood may cease to flow if the vessel reaches its closing pressure i.e. the point at which the vessel wall tone exceeds the blood pressure within.

There are three other arguments against the application of Poiseouille's formula to conditions which exist in the circulation. These are that the slip of plasma at the endothelial blood wall probably does not occur, that the length of the vessel may be insufficient for laminar flow (parabolic profile) to develop and that, for blood to flow in small vessels ($< 7\ \mu$) a certain yield stress needs to develop. This stress force (or Bingham body) is required to deform RBC's so that they can enter a vessel of smaller diameter than the cell itself. A study on the dynamic viscosity of human blood (Evans et al 1971) demonstrated that this yield force was greatest when the flow was first initiated as opposed to when an increase in flow rate occurred in an already moving volume of blood.

It is thus clear that the viscosity of fluid is a determinant of the resistance and this in turn influences the flow of that fluid. In the human body factors which increase blood viscosity may have a direct influence on tissue perfusion. Hyperviscous blood would tend to flow more slowly and there would be a

tendency to sludging (or intravascular aggregation) (Barras 1969), thrombus formation and hence tissue hypoxia so that damage may occur. If tissue oxygenation depends entirely on these mechanical factors of the blood flow, correcting the offending variable (e.g. hyperviscosity) should improve flow and hence lessen the risk of tissue damage. This may not necessarily be true and the aim of this thesis is to examine this aspect among hyperviscous babies in more detail.

# CHAPTER 2 : THE HAEMATOCRIT

## 2.1 INTRODUCTION

The haematocrit (Hct), a measure of red blood cell volume, has provided an extremely useful haematological measurement in the newborn. Besides being a useful index of other blood conditions (e.g. anaemia), it has also been used to identify babies with polycythaemia.

Since fetal physiological adaptations to intrauterine life include an erythrocytosis, the newborn has a higher Hct at birth than at subsequent stages of later life. Determination of normal values for babies is consequently necessary. Early publications of normal Hct values at birth (DeMarsh et al 1948, Guest and Brown 1957, Gatti 1967) vary considerably. Reasons for this include factors such as the method of determination, the site from which the sample was taken, the technique used, the age of the infant and the time from birth at which the umbilical cord was clamped. Other factors may also affect the result. Before reviewing normal values in babies it is appropriate to consider these various factors as they are likely to influence the final Hct result.

## 2.2 METHOD OF DETERMINATION OF Hct

The method for Hct determination, described by Wintrobe (1929) was later modified by McGovern et al (1955) so that capillary samples could be used. This micromethod is far more appropriate for use in newborns and is universally accepted today. The method is simple, reproducible and accurate. The

blood sample is drawn up into a capillary tube (usually 1,1 x 75 mm), sealed at one end and centrifuged at approximately 12 000 RPM for 5 minutes. The column of packed red blood cells is measured as a percentage of the whole column (red cells plus plasma). This percentage represents the Hct for that blood sample. In most studies (McGovern et al 1955, Oh and Lind 1966, Shohat et al 1984(a)) there is a $\pm$ 1-3% error of the observed value when the same blood sample is tested repeatedly. Approximately 1,53% to 3,22% plasma remains trapped between the red blood cells when the microhaematocrit method is used (Pearson et al 1982). Care should be taken when interpreting results from electronic particle counters (Pern et al 1979) as these values are usually lower than those derived from the capillary method. Pearson et al (1982) argue that for this reason the micromethod is more acceptable especially for the detection of polycythaemia in newborns.

## 2.3 SITE OF SAMPLING

Results from early work concerning the site from which the blood was taken caused considerable confusion. Lucas et al (1921) found that blood drawn from the longtitudinal sinus of the newborn had a higher Hct than did a heel prick sample. Haden and Neff (1924) found that red blood cell counts, cell mass and haemoglobin were uniformly higher in peripheral blood samples when compared with longitudinal sinus samples. Wintrobe (1930) concluded from his own investigations that red cell counts were not appreciably different in blood from venous or peripheral samples. It was not until 8 years later that Andersen and Mugrage (1938) clearly demonstrated a mean

capillary-venous difference of 3,36% in babies less than 3 weeks of post delivery age. In 1941 and again in 1948 DeMarsh et al demonstrated that the peripheral Hct in the newborn was higher than that of venous samples. Oettenger and Mills (1949) and later Oh et al (1966) reasoned that this considerable difference was due to peripheral venous stasis and subsequent seepage or transudation of fluid from capillary beds. Recently Ramamurthy et al (1981) studied the relationship between unwarmed heelprick, cubital vein and umbilical venous Hct levels. They showed that the mean umbilical venous Hct was 8% lower than blood sampled from the cubital vein. The capillary-umbilical vein difference was 12%. They recommended that the umbilical venous Hct, being a measure of central Hct, be used for the diagnosis of polycythaemia. Justifiably, caution is recommended. Sick, hypotensive babies have large capillary-venous differences (Oski and Naiman 1982) and may warrant a central venous line. However, as pointed out by Shohat et al (1984(a)), it seems that the invasive method of umbilical venous catheterisation for Hct measurement is not practical or justified especially in a relatively well newborn infant. The understanding therefore is that the term peripheral Hct refers to a blood sample measurement from a peripheral skin site (e.g. newborn heel) while a central Hct is one derived from venous blood (e.g. cubital vein).

## 2.4 TECHNIQUE

Another variable which may affect the Hct value is the technique of blood sampling. Venipuncture in the newborn can often be difficult as well as traumatic so that the heelprick capillary

method is preferred. There is a marked discrepancy between a heelprick Hct from a cold foot and a central venous value (Linderkamp et al 1977). Oh et al (1966) showed that this difference can be improved by warming the heel in a waterbath 40 - 42°C. They found that heel warming prior to heel puncture improved the capillary venous Hct correlation significantly. Naturally, free flow of blood should be achieved without the use of excessive squeezing pressure.

## 2.5 AGE

The recommended age for determining the Hct in the newborn is approximately 6 hours. However, Steele (1962) showed a 4% Hct rise in normal babies (cord clamped at 1 min) after 2½ hours of life. In a study by Oh et al (1966), marked changes in Hct were observed during the first 6 hours, particularly in babies who had received placental transfusion at birth. These changes were thought to be due to rapid shifts of plasma from the vascular space and to the effects of regional blood flow, especially to the gastrointestinal tract. Shohat et al (1984(a)) studied babies longitudinally from birth until 18 hours of age. They demonstrated considerable variations but specifically that the Hct peaked at 2 hours and progressively fell thereafter. Thus 20% of their study babies were polycythaemic at 2 hours but only 2% by 18 hours. In a subsequent paper, Shohat et al (1984(b)) suggested that a dynamic definition of neonatal polycythaemia related to time of sampling would be preferable. Whether this transient polycythaemia in an otherwise normal baby is of clinical significance is not clear. Alternatively, further elevation of the Hct in babies with existing polycythaemia would be undesirable.

## 2.6. TIME OF CORD CLAMPING

The role of placental transfusion is a most important factor affecting the Hct in the newborn. A detailed review of the subject by Yao and Lind (1974) illustrates many of the problems encountered with large placental transfusions and agrees that delays in cord clamping markedly influences the Hct. DeMarsh et al (1941) studied the effects of 'depriving the infant of its placental blood'. They found large differences in haemoglobin and total red blood cell counts in early and late cord clamped cases. Again, in 1942, DeMarsh et al showed a mean 7% Hct difference between early and late cord clamping. These Hct levels mirrored changes in blood volume. Usher et al (1963) measured blood volumes in babies following immediate clamping ( $\prec$ 22 sec), delayed clamping (5 min) and delayed clamping with cord stripping. There were significant elevations of the Hct to a mean of 61% in both delayed clamped groups but not in babies who had their cords clamped immediately after birth (Hct mean 44%). Yao et al (1968) measured blood volume and Hct changes with early and delayed cord clamping and related these to the use of methylergometrine in mothers. A progressive step- wise and rapid rate of placental transfusion occurred with and without the use of methylergometrine but more so in the former group. A concurrent increase in Hct was observed in babies allowed placental transfusion. Cort and Přibylová (1964) reported that the Hct of 3 hour old babies exposed to delayed cord clamping was 35% higher than the cord venous value at birth. Again Oh et al (1966) demonstrated poor peripheral vs venous Hct correlation and related this to the time of cord clamping. McCue et al (1968) showed a significant increase in

Hct at 4 and 14 hours of age after delayed cord clamping. It is interesting to note that in this study no significant difference was observed after 30 min between early and late clamping probably because significant fluid shifts had not occurred by this time. It is clear that infants who are allowed large placental transfusions become hypervolaemic and that rapid fluid shifts occur within the baby which concentrate the red cells and result in higher Hct values. Further evidence for this was reported by Pietra (1968) who showed large numbers of endothelial fenestrae in capillary vessel walls of late cord clamped infants. It was proposed that fluid leaves the vessels via these openings.

## 2.7 OTHER FACTORS

Other factors may also influence the newborn Hct. The altitude at which the gestation occurred appears to affect the Hct of the fetus. In a study from Denver, at an altitude of 1610 M (Wirth et al 1979) the incidence of polycythaemia was 4% while in Hawaii at sea level, (Wiswell et al 1984) the incidence was 1,14%. Stevens and Wirth et al (1980) compared Denver babies with those born in Norfolk, Virginia, where the incidence was 2,9% and found a significant difference between the 2 groups. They proposed that mild hypoxia at higher altitudes may stimulate erythropoietin production so increasing the Hct. Chronic cyanotic maternal heart disease probably causes fetal NP by the same mechanisms (Makhtar and Halliday 1982).

Maternal-fetal transfusions have been shown to effect the newborns' Hct. Michael (1961) reported 3 cases with elevated

Hct (73% - 80%) where the babies had an excess of maternal erythrocytes. Andrews and Thompson (1962) and Walsh (1962) also found evidence in a further 3 cases. In all cases the babies were clinically plethoric with polycythaemia.

The Hct levels in adults have been shown by Ehrly and Jung (1973) to demonstrate circadian rhythm. Explanations for these variations are not clear nor is it clear whether these variations occur in newborns.

In conclusion, although the Hct is a convenient neonatal haematological measurement, care must be exercised in interpretation of results. This is especially true in the diagnosis and management of polycythaemia.

## 2.8 PUBLISHED NORMAL VALUES

Table 1.1 shows published data for normal newborn Hct values in the first 10 days of life. Where possible the site of sampling and the delay in cord clamping are given.

TABLE 2.1

NORMAL HAEMATOCRIT (%) VALUES IN THE NEWBORN

| AUTHOR | CORD | DAY 1 | DAY 2 | DAY 3 | DAY 4 | DAY 5 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | COMMENTS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Andresen (1938) | Venous $54,92 \pm 6,19$<br><br>Peripheral $58,28 \pm 6,3$ | | | | | | | | | | | Blood sampled between 30 min to 19 days |
| Waugh (1939) | | 51,3 | | 49,15 | | 48,7 | | 46,8 | | 45,9 | | Source not stated |
| DeMarsh (1942) | $51 \pm 4,6$ | $53 \pm 2,9$<br><br>$61 \pm 2$ | | $51 \pm 5,1$<br><br>$60 \pm 3,5$ | | | | | | | | Early cord clamping<br><br>Late cord clamping |

| AUTHOR | CORD | DAY 1 | DAY 2 | DAY 3 | DAY 4 | DAY 5 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | COMMENTS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DeMarsh (1948) | 52 | 52 ±3,9<br>60 ±2,71 | | 50 ±5,15<br>59 ±4,34 | | | | | | | | Early cord clamping<br>Late cord clamping |
| Guest (1957) | 52,3±0,7 | 58,2 ±0,9 | | 54,5 ±0,8 | | | 51,9 ±0,8 | | | | | Blood sampled from fontanelle |
| Zinkham (1963) | | 62 ±0,6 | 59 ±6,8 | 55 ±6 | | 55 ±6 | | | 52 ±6,8 | | | Unwarmed capillary blood |
| Moe (1965) | | 65,9 ±7,5 | | | | | | | | | | 2-6 days heel blood |
| Gatti (1967) | | 62,9 ±3,2 | 61 ±2,9 | 60,5 ±2,7 | 58 ±2,5 | 56,6 ±2,5 | 56,1 ±2,3 | 56 ±2,6 | 55,5 ±2,6 | 55,2 ±0,4 | 53,7 ±2,5 | Unwarmed capillary blood. Uncontrolled cord clamping |
| Mathoth (1971) | | 61 ±7,4 | 60 ±6,4 | 62 ±9,3 | 57 ±8,1 | 57 ±7,3 | 54 ±7,2 | 56 ±9,4 | | | | Warmed capillary blood. Uncontrolled cord clamping |

| AUTHOR | CORD | DAY 1 | DAY 2 | DAY 3 | DAY 4 | DAY 5 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | COMMENTS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Effiong (1976) | | 60,8 ±7,2 | 58,1 ±6,3 | 55,0 ±6,6 | 54,4 ±7,4 | 52,4 ±6,1 | 50,6 ±6,4 | | | | | Cord clamped at 1 min. Warmed heel capillary |
| Shohat (1984(a)) | 53,4 | 51,8 | | | | | | | | | | Cubital vein blood |

# CHAPTER 3 : NEONATAL POLYCYTHAEMIA

## 3.1 INTRODUCTION

During the last twenty years, and particularly in the last 10 years, considerable attention has been given to the subject of neonatal polycythaemia (NP). Of particular interest has been the allied hyperviscous state which so commonly accompanies the abnormally high Hct value. Neonatal polycythaemia has been variously defined as a venous Hct value in excess of 60% (Humbert et al 1969, Kontras 1972, Sommer and Kontras 1971), 65% or more (Gross et al 1973, Phibbs 1977, Wirth et al 1979, Stevens and Wirth 1980) and 70% (Dunn 1970). A Hct of 65% or greater is now generally accepted as the definition of NP (Oski and Naiman 1982, Shohat et al 1984(b)). This definition is based on the findings of a virtually straightline relationship between viscosity and Hct up to 65% whereas, thereafter, there is an exponential increase in viscosity for each unit change in Hct (Giombi and Burnard 1970, Rand et al 1964(a), Mackintosh and Walker 1973). Blood viscosity doubles between Hct 50% and 70% and trebles between 50% and 80%. Shohat et al (1984(b)) argue that the Hct level at which NP is defined depends upon the time of blood sampling and also that the viscosity Hct relationship is not a straight line at low levels of Hct. They suggest a venous Hct of 71% or more at 2 hours and 68% or more at 6 hours to be the definition of NP. Internationally, the definition of polycythaemia is a Hct level that is greater than or equal to 65% and we should await confirmation of the findings of Shohat et al before changes to the definition are made. These arbitrary definitions are used to identify infants at risk of polycythaemia. However, it is not the excess of red cells alone

that is harmful to the neonate but the hyperviscosity state that usually coexists with it.

As mentioned earlier, it is important to establish whether the infant is truly polycythaemic or not and if so whether the high Hct is a reflection of conditions prevailing in the central circulation of the baby. A capillary sample from a peripheral cold limb is a poor measure of Hct (Oh et al 1966) and a central venous sample should always be taken if polycythaemia is suspected. Problems arise as to what constitutes a central venous sample and what is representative of organ capillary Hct (especially brain). Ramamurthy and Brans (1981) recommended that all infants be screened using a warmed heelprick capillary Hct. If the Hct value is found to be $>$ 70% a peripheral venous Hct level should be measured and if $>$ 65% an umbilical vein sample should be obtained. In their study, treatment of NP was instituted when the umbilical vein Hct was $>$ 63% (viscosity $>$ 15 cps at 11,5 $sec^{-1}$). Most other studies have used the cubital vein Hct as representative of the central Hct. Clearly, the use of this site is much less invasive and more convenient in actual practice. Other sites including the longitudinal sinus (Lucas et al 1921, Haden and Neff 1924), the femoral vein, scalp vein (Oh et al 1966) and jugular vein have been used. Although not ideal, most workers today would use the cubital vein whenever possible. It must be stressed that the detection of NP is only a step in the total evaluation of the infant. Ideally, blood viscosity studies should be done if polycythaemia is diagnosed.

## 3.2 CAUSES OF POLYCYTHAEMIA

The causes of NP can be divided into ACTIVE and PASSIVE forms. In babies with the ACTIVE form, the fetus is thought to produce an excess of red blood cells while in the PASSIVE form the fetus receives an excess of red blood cells by transfusion. Although this classification is convenient, the actual cause in individual babies is usually obscure or difficult to establish.

### 3.2.1 Active Form

#### 3.2.1.1 Chronic Hypoxia

The active form of polycythaemia is thought to result from an excess of erythropoietin which stimulates the erythropoietic system to produce red blood cells (Finne 1966). Most common in this category are those fetuses exposed to chronic intrauterine hypoxia. Gruenwald (1963) was amongst the first to describe NP as a result of chronic hypoxia in utero. Haworth et al (1967), Humbert et al (1969) and Wirth et al (1979) attributed the higher incidence of NP in small for gestational age babies to the same reason. Infants born following prolonged intrauterine hypoxia and with NP have increased numbers of reticulocytes and nucleated red blood cells (Raynaud et al 1972) in their peripheral circulation at birth. These cells disappear rapidly so that at about the fourth day of life few are evident. Surprisingly, erythropoietin levels are also low at this time (Wiswell et al 1983). It would appear that once tissue hypoxia has been relieved, erythropoietin production of cells is rapidly reduced since enhanced oxygen carrying capacity is no longer necessary (Halvorsen 1963). Typically, the most common form of active NP is seen in the small for gestational age infant.

These babies are often near term or are post-term. NP is uncommon in babies of less than 34 weeks gestation (Wirth et al 1979). This active form of erythrocytosis which results from intrauterine hypoxia and erythropoietin stimulation is the most common cause of NP.

3.2.1.2 Other Causes

Other causes of active NP in which hyperactive intrauterine fetal erythropoiesis appear to be responsible include Trisomy 21 (Lappalainen and Kouvalainen 1972, Naveh et al 1971), Trisomy 18, Trisomy 13 (Baum 1967), neonatal thyrotoxicosis (Bussmann et al 1977), congenital adrenal hyperplasia (Gold and Michael 1959), and maternal propranalol therapy (Gladstone et al 1975). Babies born to diabetic mothers frequently have polycythaemia. These babies have been found to have raised erythropoietin levels which are also thought to be the result of chronic intrauterine hypoxia (Widness et al 1981). It would seem likely that the polycythaemia frequently seen in the Beckwith-Wiedemann syndrome (Smith 1970) is also due to excess erythropoietin. It is assumed that the above conditions cause NP by excessive erythropoietin stimulation but this has not been proven in all instances

3.2.2 Passive Form

The Passive form of NP results from a transfusion of blood either from the placenta, another fetus (twin) or from the mother. Dehydration or an excessive therapeutic blood transfusion are rare causes. In cases of neonatal transfusion it has been shown that the hypervolaemic state is rapidly corrected by fluid shifts from the vascular compartment. This

and Sutherland 1970). Significant transfusions of blood may occur either chronically during pregnancy or more acutely at delivery. In both situations the recipient fetus may be polycythaemic and the donor anaemic. It is estimated that significant twin-to-twin transfusions occur in 15-33% of all monochorionic twins (Rausen et al 1965, Corney and Aherne 1965). The management of both the donor and the recipient may be extremely difficult (Shorland 1971).

3.2.2.3 Maternofetal Transfusion

The transfer of blood from the mother to the fetus is now a well recognised phenomenon (Hedenstedt and Naeslund 1946, Naeslund and Nylin 1951, Mengert et al 1955, Macris et al 1958). Evidence for this has been the demonstration of maternal erythrocytes in the infant's blood, a low level of fetal haemoglobin, the presence of beta 2 M globulin or beta 2A globulin and an elevated Hct, Hb and red cell count at birth. Michael and Mauer (1961) were the first to point out that these infants may be polycythaemic at birth. The mechanism for this maternal - fetal transfusion is not clear but it has been suggested that a break in fetal placental capillaries allows maternal blood to pass from the intervillous space to the baby (Michael and Mauer 1961). Haematocrits in excess of 75% have been observed in these infants (Shorland 1971).

Whatever the mechanism, both active and passive forms of NP result in abnormally high Hct values. These polycythaemic infants are at risk of neonatal hyperviscosity syndrome which may result in clinical manifestations harmful to the baby.

Hyperviscosity would appear to be the common pathway by which both morbidity and mortality in these infants occur.

# CHAPTER 4 : HYPERVISCOSITY

## 4.1 INTRODUCTION

The effect of the viscosity of the blood plays a major role in the perfusion of body tissues and on their subsequent normal function. Hyperviscous states in the newborn are associated with pathological conditions some of which can be life threatening. A clear definition of what constitutes hyperviscosity in the newborn is therefore important. It is also necessary to understand the causes of hyperviscosity in these babies. The appropriate management of affected infants is controversial and especially so for those infants who have no signs or minor clinical signs. This issue forms the basis for this thesis.

## 4.2 NORMAL VALUES

A number of studies have been undertaken using a Wells-Brookfield microviscometer to define the normal limits of blood viscosity in the newborn. Considerable variations have been found for each population group studied, and these differences usually reflect and are affected by the site and the time of blood sampling. In a study of 94 normal infants Sommer and Kontras (1972) measured cubital or dorsal hand venous blood viscosity between shear rates 11 - 212 $sec^{-1}$. The infants were studied daily for 3 days. Fairly high mean ( and SD) normal values were obtained. Although the authors claim these were normal infants, some babies had Hct values as high as 77% and were clearly hyperviscous. Mackintosh and Walker (1973) in a study of 110 normal term babies defined viscosity between

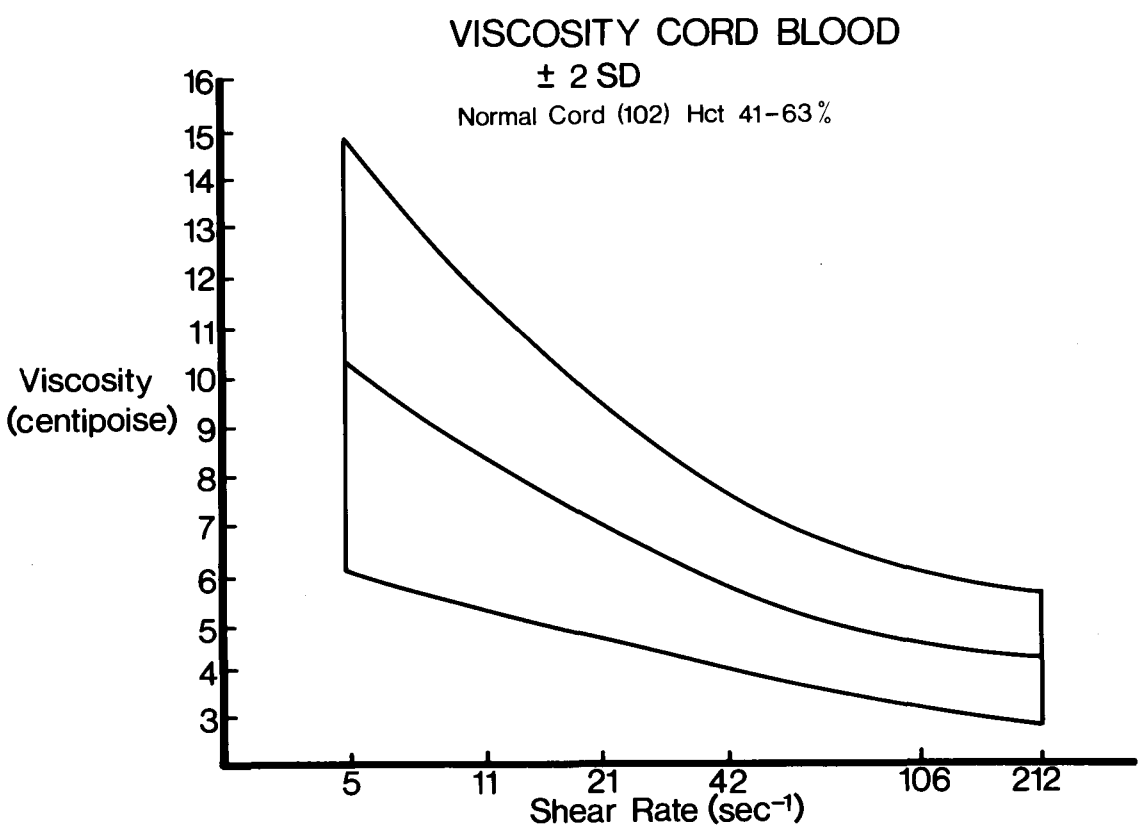
shear rate 11,5 and 230 $sec^{-1}$ in venous blood. The mean values for viscosity increased from 5,5 cps at 232 $sec^{-1}$ to 11,2 cps at 11,5 $sec^{-1}$. The mean Hct was 55%. These values are within an acceptable range but no information is given of the age of the baby since birth or the method of blood sampling.

Bergqvist (1974) examined 20 normal neonates during the first week of life. Results were again very different from those of previous studies. Gross et al (1973) examined cord blood viscosity at birth. In all they studied 102 cord blood samples using a Wells-Brookfield microviscometer. Unfortunately, the data was published in graph form and thus exact values are difficult to gauge. However, these values have been universally accepted as a reasonable standard for cord blood viscosity in the newborn (See Figure 4.1).

Bergqvist (1974) also examined cord blood samples in 20 normal babies. Although the results are different from those of Gross et al, they are less discordant than the results of other publications. Recently, Shohat el al (1984(a)) examined 50 normal babies taking cord blood and then venous samples for the first 18 hours of life. They show significant variations in viscosity over this period which again differ from published results obtained when babies are older. It is thus clear that although useful, the results of normal blood viscosity values from different population groups vary considerably and that caution is necessary when these results are used. It is appropriate therefore, to determine one's own normal values for the population studied, and to use these to determine those

FIGURE 4.1

VISCOSITY (cps) OF UMBILICAL CORD BLOOD AT VARIOUS SHEAR RATES (AFTER GROSS ET AL 1973)




Gross et al 1973.

infants at risk of hyperviscosity. A second consideration is to define what constitutes the upper limit of normal viscosity. Clinical signs are not inevitable in all hyperviscous babies (Høst and Ulrich 1982) so that other markers must be sought. By convention, the use of 2 standard deviations from the mean of a normal population is acceptable (Gross et al 1973. Mackintosh and Walker 1973, Goldberg et al 1982) and most studies have used this calculation to define normal values of viscosity. The mean $\pm$ 2 SD is calculated for the whole blood viscosity at each shear rate tested and these values are used to define the upper and lower limits of normality.

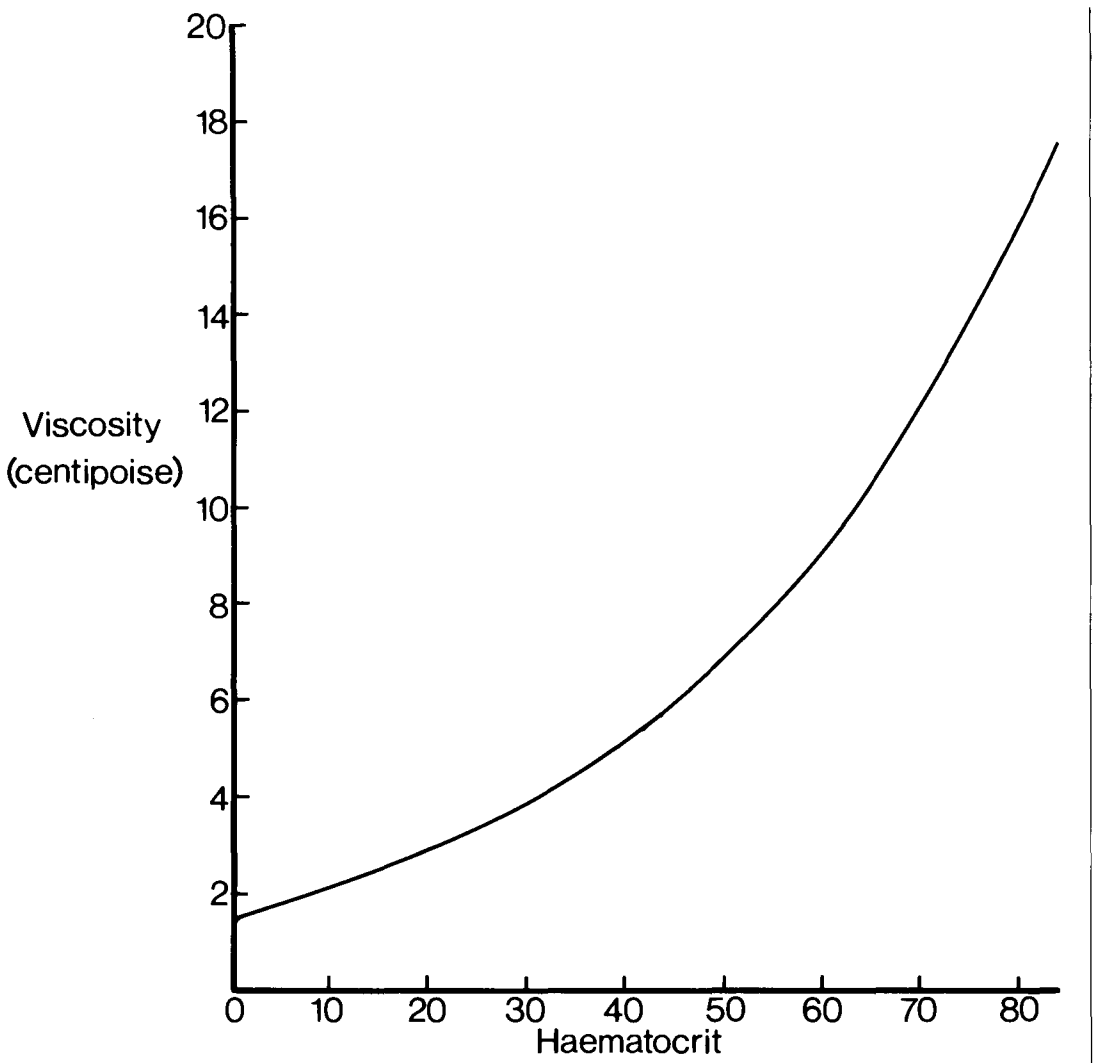
## 4.3 CAUSES OF HYPERVISCOSITY

Several factors are responsible for hyperviscosity in newborn blood. The first, as discussed earlier, is the velocity of flow of the blood. A second and major contributing factor, is the Hct level in the blood. At any shear rate tested the viscosity of whole blood will be low when the Hct is low. As the percentage Hct increases there is an exponential increase in blood viscosity and this becomes most marked when the Hct is $\geqslant$ 65% (Shohat et al 1984(a)) (See Figure 4.2).

This influence of the Hct on the viscosity is the main reason for newborn babies with polycythaemia becoming hyperviscous (Kontras 1972). Hyperviscosity of whole blood can be attributed to many causes but in the newborn the absolute number of RBC's plays the major role in determining the viscosity of the blood sample. Consequently, the treatment of hyperviscosity in the newborn is mainly directed towards reducing the numbers of RBC

FIGURE 4.2

WHOLE BLOOD VISCOSITY WITH VARYING HAEMATOCRIT AT SHEAR RATE 46 $sec^{-1}$



within the circulation. The terms polycythaemia and hyperviscosity are frequently used interchangeably. This practice should be avoided as the two are not synonymous. Polycythaemic neonates are usually hyperviscous but not all hyperviscous babies have polycythemia (Black and Lubchenco 1982(b)). For the purpose of this study it is assumed that, in the main, the hyperviscosity is related to the haematocrit and so the term neonatal polycythaemia associated hyperviscosity is used (NPHV).

Another factor which may significantly influence the blood viscosity is the ability of the red blood cell to alter in shape. Red cell fluidity depends on there being both a flexible membrane and liquid in the cell interior. The biconcave resting shape of the RBC is a result of surplus membrane and this feature enhances cell flexion. Cell fluidity can alter for 2 reasons, either the membrane becomes stiff or the internal content (the cell fluid) becomes too viscous (Schmid-Schönbein et al 1971). If cells are made rigid then flow will cease at Hcts over 60% (Chien et al 1970(a), Dintenfass 1968) and the blood behaves as a solid at a Hct of 65% or more. Gross and Hathaway (1972) compared fetal and adult blood cell deformability by passing samples through a micro-filter. Neonatal blood was found to be significantly less deformable than adult blood. This inability of red cells to deform correlates inversely with viscosity. Since deformability of cells is essential for the 'tank-tread' like motion of the RBC membrane around the cell contents, conditions such as sickle cell disease (Chien et al 1970(b), Dintenfass 1964), spherocytosis (Murphy 1967) and hyperosmolar states (Giombi and

Burnard 1970) will decrease membrane plasticity. These conditions all increase the viscosity of blood by decreasing the ability of RBC's to deform as they pass through the microcirculation.

Temperature also has a marked effect on blood viscosity. Baum (1966) was able to show that a one degree fall in temperature was associated with 2,5% increase in blood viscosity. In polycythaemic states low temperatures have a pronounced effect on viscosity (Reemtsma and Creech 1962) and these effects are more pronounced at low shear rates (Barbee 1973). It would appear that low temperatures exert their effect on the cell surface and not the cell contents (Murphy 1967).

The acidity or alkalinity of the blood is another factor which has an effect although slight on viscosity (Rand et al 1968). These effects are thought to be caused by cellular as opposed to plasma factors. Bacigalupo and Saling (1973) found that the Hct in cord blood samples increased with acidity and proposed that this was due to haemoconcentration which had resulted from capillary leakage of plasma from the vascular compartment. Murphy (1967) also concluded from studies on normal erythrocytes that viscosity increased when the pH was lowered from 8,0 to 6,8. This level is very low but is not uncommon in some clinical conditions in the newborn.

An additional factor thought to play a role in blood viscosity is the osmolality of the blood. Hypertonicity of plasma has been shown to increase viscosity to a marked degree (Rand and

Lacombe 1965, Rand et al 1964(b)). This occurs only when crenated RBC's are present and again may be due to osmolar effects in the RBC resulting in membrane rigidity.

Changes in plasma constituents are not a common problem in the newborn. Hyperviscous states are reported in adults with multiple myeloma (Lindsley et al 1973) and in animal experiments with induced hypercholesterolaemia (Newman and Twinn 1973). The nature of plasma proteins may play a significant role. The concept of cell-protein-cell bridges and that of rouleaux formation have been studied by Wells (1970) and by Schmid-Schönbein et al (1969). The contribution of plasma viscosity in the newborn with polycythaemic hyperviscosity is minimal (Gross et al 1973). Newborns, and particularly preterm infants, tend to have a low plasma viscosity (Linderkamp et al 1984, Reinhart et al 1985). The addition of adult plasma to neonatal red cells increases blood viscosity. Thus logically the infusion of adult plasma into a NP newborn without the removal of red cells would not be beneficial. Hyperfibrinogenaemia has been implicated as a cause in a study in growth retarded fetal lambs (Pickart et al 1976) but has not been reported to cause hyperviscosity in the human newborn.

## 4.4 CLINICAL SIGNS

A wide range of clinical signs have been reported in hyperviscous polycythaemic neonates. Whether they are all attributable to the hyperviscosity or to the polycythaemia or both is not clear (Oski and Naiman 1982). Signs vary in affected infants from none at all to those who have central

nervous system manifestations (Gross et al 1973), cardiovascular abnormalities (Gatti et al 1966), and gastrointestinal complications (Hakanson and Oh 1977). Metabolic disturbances are also reported (Gross et al 1973).

Amongst early records of clinical signs Wood (1959) attributed apnoea, cyanosis, lethargy, poor feeding and convulsions to polycythaemia in 2 infants. Both responded to partial plasma exchange transfusion. Polycythaemia was found to be the common aetiology of 10 cyanotic newborns who presented with congenital heart disease (Gatti et al 1966). Three of these cases had myoclonic jerking, one developed a hemiparesis and 2 were subsequently neurologically normal. Humbert et al (1969) in a study on 4 small for gestational age polycythaemic babies (viscosity was not measured) documented respiratory difficulties, priapism, hypoglycaemia and hypocalcaemia. Residual neurological damage attributable to hyperviscosity was observed in 3 out of 16 cases by Baum (1966 and 1967). Amongst the signs observed by Kontras (1972) in a study of 15 hyperviscous babies, respiratory distress, seizures, lethargy and vomiting were noted. Gross et al (1973) reported signs in 18 affected babies. Cyanosis and plethora were most common, neurological signs (jitteriness, abnormal EEG and seizures) were present in 72% cases and 50% had cardiopulmonary signs. Necrotizing enterocolitis has been seen in hyperviscous infants (Leake et al 1975, Hakanson and Oh 1977, Black et al 1982(c), Black et al 1985(b)).

Mackintosh and Walker (1973) identified 19 hyperviscous babies of which 4 were free of signs. Of the remaining 15, 4 had cyanosis, 11 had cerebral signs and 2 had respiratory distress. Four were small for gestational age. Recently Goldberg et al (1982) published the results of careful observations on 20 hyperviscous infants. Generally the affected babies were lethargic and hypotonic at birth but at 8 months of age there were 6 cases with spastic diplegia and 3 cases with developmental delays.

Metabolic disturbances have also been reported in association with hyperviscosity. Hypoglycaemia was reported in 3 of 11 hyperviscous patients by Humbert et al (1969). Significant hypoglycaemia was also frequent (33%) in the study by Gross et al (1973). Prospective screening in babies with NPHV revealed 30 out of 111 cases (Black et al 1982(a)) to have hypoglycaemia. The occurrence in other studies was infrequent (Gross et al 1973) or not a problem (Goldberg et al 1982). Gross et al (1973) found half of their study infants to have bilirubin levels $>$ 12 mg %. This association was also reported by Kresky (1964) but no greater incidence was seen in another study of 205 polycythaemic patients when these were compared with controls (Black et al 1982(b)).

Thrombocytopaenia was observed in 8 out of 18 hyperviscous babies (Gross et al 1973) and recently in 5 more patients (Goldberg et al 1982). Ongoing disseminated intravascular coagulation has not been found to be a problem (Henriksson 1979).

Renal function has also been shown to be impaired with NPHV. Glomerular filtration rate and tubular reabsorption of sodium and potassium was found to decrease in 12 puppies made polycythaemic (Kotagal et al 1977). Reduced renal function (GFR and water excretion) was shown to improve in 10 hyperviscous babies once they were treated with partial plasma exchange transfusion (Aperia et al 1974). Serum concentrations of 1,25-dihydroxy-vitamin D and 24,25 dihydroxy-vitamin D were found to be lower in NP babies (Alkalay et al 1985), the postulated mechanism being decreased renal blood flow.

Blood flow to various other organs has been reported to be diminished in polycythaemic or in hyperviscous states. Blood flow to the gastrointestinal tract was measured in 12 chronically catheterised fetal lambs while the Hct was progressively increased isovolaemically from 12% to 45% (Fumia et al 1984). A decrease in both gastrointestinal blood flow and oxygen delivery with increasing Hct was observed. Maximal oxygen delivery was achieved by increasing Hct to 33% beyond which a reduced oxygen delivery was observed. In another study, Kotagal et al (1977) worked with puppies made polycythaemic and hypervolaemic. They found that although there was a drop in cardiac output the fall in flow to the GIT was out of proportion to that which would have been expected from the cardiac findings. The above 2 studies provide evidence for the redistribution of cardiac output in conditions of NP such that brain, heart and adrenals benefit at the expense of the GIT, kidneys and other organs. Several reports of necrotising enterocolitis (Black et al 1985(a), Black et al 1985(b), Gunn

and Outerbridge 1977, Hakanson and Oh 1977, Leake et al 1975) associated with hyperviscosity also testify to a likely association between these two events.

It would also appear that peripheral blood flow is diminished by the presence of hyperviscosity but only in certain circumstances. Bergqvist and Zetterström (1974) measured resting blood flow in the limbs of 18 infants. They could not demonstrate a correlation between viscosity and blood flow or between viscosity and peripheral resistance. Isovolaemic haemodilution did not alter resting flow either . However, in another paper Bergqvist (1975) has also shown that maximal flow diminishes with increasing Hct so that the reserve capacity for flow in muscle is less with polycythaemia. Contrasting these results Le Blanc et al (1982) have studied polycythaemic hyperviscous puppies also while at rest. They were able to show a 170% increase in peripheral vascular resistance when the Hct and blood viscosity were increased to pathological levels. This, together with a 50% decrease in cardiac output, would indicate that the blood flow to the periphery of the animal would be reduced. One would assume therefore that stasis might be a considerable problem in babies with NPHV. This has not been found to be the case and only one report (Papageorgiou and Stern 1972) describes peripheral venous thrombosis with gangrene of the index finger in a NPHV baby.

The effect of NP and HV on the heart and lung radiographs have also been studied in 20 hyperviscous infants by Wesenberg et al (1977). Seventeen babies were found to have increased pulmonary

vascularity, hyperaeration and alveolar infiltrates but showed no clinical signs when they were examined. These changes decreased following treatment with partial plasma exchange transfusion. In another study Oh et al (1966) found a direct correlation between Hct and simultaneously measured systolic blood pressure. This correlation was seen in babies 4 hours old but disappeared by 24 hours of age. Echocardiographs have also been used (Geierman et al 1979) and this together with radiological evidence has shown the presence of cardiac failure (Lanning et al 1977) in babies with NP.

The effects of high blood viscosity on pulmonary vascular resistance have been studied by Tyson and Fender (1971). Using adult dogs they were able to show that there was a direct relationship between elevated Hct and pulmonary vascular resistance. Cardiac output also decreased with increasing Hct. Fouron and Hêbert (1973) studied these haemodynamic changes in polycythaemic lambs. At a Hct of 70%, right-to-left shunting of blood also occurred as a result of high pulmonary vascular resistance. In an editorial, Gersony (1973) briefly reviews hyperviscosity and mentions a 16 hour old NPHV baby who underwent haemodynamic studies. Elevated pulmonary resistance with right to left shunting through the foramen ovale and ductus arteriosus was also shown angiographically in this infant. Recently Murphy et al (1985) studied 19 NP infants using echocardiography and also showed increased pulmonary resistance which resolved with PPET.

In conclusion, it would appear that the main effects of HV on the cardiovascular system are increased pulmonary artery

resistance, cardiomegaly, decreased cardiac output and cardiac failure.

The pathophysiological disturbances seen in hyperviscous babies suggest that the neurological sequelae that result may originate from brain ischaemia and tissue hypoxia. These results are thought to be due to increased viscosity and subsequent sludging or cellular aggregation of blood. Occasional reports describe intracranial haemorrhage (Miller et al 1981), hydranencephaly (Koffler et al 1974) and multiple cerebral infarcts (Amit and Camfield 1980) in NPHV patients. Coupled with these findings is the concern that subclinical damage may result and that CNS problems will only manifest in later life. Several such instances are reported (Black et al 1982(a), Baum 1966, Baum 1967, Goldberg et al 1982). With these misgivings in mind, it is appropriate to examine current knowledge of the pathophysiological events that occur in the brain due to elevated Hct and viscosity.

Changes in cerebral blood flow (CBF) in association with Hct and viscosity are reported in animal studies, human adults and in newborn infants. Kotagal et al (1977) working with newborn puppies found a decrease in CBF in polycythaemic hypervolaemic dogs. This occurred despite an increase in the percentage of cardiac output flow to the brain. Hypervolaemia alone did not affect CBF but the polycythaemia increased cerebral vascular resistance and hence decreased CBF. In adults CBF was increased by 50% (Thomas et al 1977) when the Hct was reduced from 49% to 42% by venesection. Wade (1983) also studied adults with HV due

to hypoxic lung disease and examined their response to venesection. It was suggested that changes in CBF occurred as a result of reflex homeostatic mechanisms initiated by the brain. These mechanisms would act to maintain oxygen transport in the face of reduced oxygen content. In their study of 20 adults following venesection there was a significant rise in $PaO_2$, a fall in oxygen content and 7% increase in $O_2$ transport to the brain. In an earlier study Wade et al (1981) had shown a 21% increase in CBF following venesection but no change in oxygen carriage. Recently, Brown and Marshall (1985) confirmed the importance of blood arterial oxygen content in the determination of CBF and demonstrated that regulating mechanisms can maintain cerebral oxygen transport despite increased plasma and whole blood viscosity. Again Lahtinen and Kuikka (1983) were also able to demonstrate improved CBF following venesection. In hyperviscous newborn babies Rosenkrantz et al (1982) showed that CBF and vascular resistance fell significantly following exchange transfusion.

These studies therefore show decreased CBF in the presence of NPHV but do not examine oxygen utilisation at a cellular level. The question of decreased CBF and viscosity was considered by Friedland (1979). It was suggested that CBF may not be related to viscosity but may be due to metabolic control mechanisms intrinsic to the cerebral circulation. Evidence for this stemmed from considering the Fähraens-Lindquist effect of viscosity lowering in small vessels. Attention, therefore, needed to be directed towards oxygen transport, extraction and consumption.

A study in NPHV puppies (Le Blanc et al 1982) showed that cardiac output was maintained so that oxygen transport was appropriate for oxygen uptake by the tissues. Fumia et al (1984) working with fetal lambs was able to show that in the face of Hct changes, blood flow was regulated so that $O_2$ delivery to brain, heart and adrenals remained stable. In another study, fetal lambs made hyperviscous (Tenenbaum et al 1983) showed a decrease in umbilical blood flow such that $O_2$ delivery also decreased. However, they did find that $O_2$ consumption was not changed, the reason being that there was an increased extraction of $O_2$ by the fetus. Rosenkrantz et al (1984) in a unique study on chronically catheterised lambs were able to manipulate oxygen content in the presence of polycythaemia and hyperviscosity. They found that the total blood flow to the brain diminished as the lambs were made polycythaemic and hyperviscous by an exchange transfusion with packed red cells. The oxygen content of the blood had increased significantly. After an infusion of nitrite the presence of methaemoglobin caused the oxygen content to drop to pre-exchange levels. The total brain blood flow returned to pretransfusion levels. Calculated oxygen delivery had remained constant throughout the study for the whole brain. These results indicate that the reduction of cerebral blood flow in polycythaemia and hyperviscosity is a physiological response to increased arterial oxygen content and not a result of hyperviscosity. Thus, where $O_2$ content of blood is elevated (polycythaemia) the CBF diminishes proportionally since $O_2$

delivery and extraction remain adequate.

In a study of NP and HV on cutaneous blood flow Waffarn et al (1984) studied 10 hyperviscous neonates prior to and after PPET. Using transcutaneous $pO_2$ and $pCO_2$ and by measuring cutaneous blood flow they were able to show that $pO_2$ and $pCO_2$ were in the normal range in the hyperviscous state and remained unchanged following exchange transfusion. This occurred despite a significant increase in cutaneous blood flow following PPET. This study again argues in favour of tissue $O_2$ requirements being the regulator of blood flow in hyperviscous states.

These findings throw new light on the pathogenesis and the haemodynamic changes in NPHV.

## 4.5 TREATMENT

From the previous review it is clear that NPHV can be associated with both severe and minor pathological clinical signs. It is also possible that there may be no signs at all. The mechanisms for the signs are not clear but poor tissue perfusion, sludging and intravascular aggregation, red cell deformability and/or tissue hypoxia could all be responsible. Despite the gaps in our knowledge most neonatal physicians would offer haemodilution therapy to hyperviscous babies with severe signs. There seems little doubt that this is of benefit to these neonates and is the accepted management at most newborn centres.

However, the majority of babies with polycythaemia and hyperviscosity appear clinically well or have only minor signs. It is not certain that in all of these relatively unaffected babies haemodilution is necessary or in fact justified. It is also possible that the condition that caused the NPHV in these infants is the underlying reason for the presence of pathological signs and that therapy would make little or no difference to the outcome in these babies.

Several early reports on the management of HV in babies were anecdotal. Wood (1959) treated 2 symptomatic infants by venesection followed by the administration of intravenous plasma. Both babies improved and were clinically well when discharged home. Gatti (1967) studied 10 cases with transient cardiorespiratory distress. Two were treated by phlebotomy and responded well while the remaining 8 who were not treated recovered spontaneously over a 2 week period. However, neurological sequelae did occur in 2 of these infants. Kontras (1972) treated 8 NPHV patients by phlebotomy and all showed symptomatic improvement. A seven month follow-up assessment of one of these babies showed normal development. The outcome of the others was not mentioned.

Mackintosh and Walker (1973) treated 6 of 19 NPHV babies with partial plasma exchange transfusion (PPET). There was a regression of symptoms within 8 hours in the treated babies as opposed to the slower resolution of symptoms over 2 to 3 days in the milder cases who did not receive active treatment. One treated infant was later found to be microcephalic and severely

mentally retarded. The remaining 19 babies were not exchanged as their condition gave no cause for concern. Emphasis was placed on treating only those HV babies with clinical signs.

Gross et al (1973) treated 12 of 18 symptomatic infants using PPET. Signs included cyanosis, seizures and cardiorespiratory problems. Seven infants showed immediate improvement. At subsequent examination (7 to 23 months of age) 2 exchanged and 2 non-exchanged infants had significant neurological abnormalities.

In a paper from Denver, Black et al (1982) identified 111 polycythaemic patients. Forty-two of these were treated with PPET (the cases were not randomised). A matched control was found for each study baby. Laboratory data and neurobehavioural assessment data were collected until the children were 3 years of age. At birth the hyperviscous babies had a higher frequency of growth retardation, hypoglycaemia, symptomatic tachypnoea, cyanosis and necrotizing enterocolitis. Follow-up between 1 and 3 years revealed that 15% of the HV patients had developmental delays. Twenty one percent revealed gross motor delays and this was significant ($p < 0,005$) when compared with the controls. A significant number of HV patients had neurologic abnormalities. In summary, 43% of patients who received exchange transfusion, 35% of the non-exchanged and 11% of control children had one or more delays when examined at follow-up. This study identifies hyperviscosity related neurodevelopmental delays in affected infants. It does not attempt to evaluate the efficacy of PPET and no recommendations in this regard are made by the authors.

Other published studies have reported organ function improvement following treatment. Aperia et al (1974) showed improved glomerular filtration rate following haemodilution in 10 NPHV babies. Wesenberg et al (1977) reported improvement of abnormal findings on chest radiographs following PPET. Gersony (1973) was able to show a fall in peripheral vascular resistance in NPHV babies who were given oxygen alone! Gunn and Outerbridge, (1977) from experience with a case of polycythaemia associated necrotizing enterocolitis, argued that all cases, whether symptomatic or not, should receive PPET.

Two studies both from Denver Colorado have addressed the issue of the treatment of NPHV in more depth. These papers both present data to determine whether affected babies benefit from PPET. The studies are pertinent to the concepts formulated for this thesis and although some of their findings are similar, the conclusions and hence the recommendations with regard to management differ.

In the first paper Goldberg et al (1982) screened babies for polycythaemia and identified 20 NPHV patients. These infants were randomly assigned to receive PPET or not be exchanged. A control group of babies with a normal Hct was included for comparison. Babies were examined during the first 3 weeks of life and again at 8 months of age. The results showed that there were more NPHV babies with hypoglycaemia, thrombocytopaenia and proteinuria than there were in the controls in the first 3 days of life. The affected babies could not be grouped according to whether they had treatment (PPET) or not.

Amongst the investigations done, a frequent feature was increased vascular markings and cardiomegaly on the chest roentgenogram. Neurobehavioural studies at up to 2 weeks of age using the Brazelton Neonatal Behaviour Assessment Scale (NBAS) and Prechtl scales clearly identified NPHV babies from the controls. There were more abnormal scores in the NPHV groups than in the controls. Treatment with PPET did not initially separate babies in the two NPHV groups. However, as time progressed both the behavioural and neurologic state of the exchanged babies improved while the non-exchanged infants remained symptomatically abnormal. When examined at 8 months of age, both of the groups that had been HV at birth had a higher incidence of neurological abnormalities. The incidence amongst those who had been exchanged was less (50%) than those not exchanged (67%). This difference was not statistically significant ($p > 0.05$). Seventeen percent of the control babies were neurologically abnormal. Although no severely handicapped children were found in this study, there was a 40% loss of subjects at the 8 months follow-up which may have affected the results. An important observation from this study is that NPHV is associated with neurologic abnormalities but that treatment with PPET does not necessarily alleviate these problems.

In a second paper, Black et al (1982(c)) randomised 94 HV patients to treatment with PPET or to being observed only. A group of matched controls was again included for comparison. Gastrointestinal symptoms and necrotizing enterocolitis were more common in exchanged babies. Brazelton NBAS examinations

done at the time of diagnosis showed no differences between the HV patient groups. Mental and motor examination of the NPHV infants at 1 year of age did not differ from the controls but speech was delayed in the NPHV groups. At 2 years NPHV patients had more motor delays and neurological diagnoses in general and these abnormalities were more common amongst non-exchange babies. This article argues for the use of PPET in babies with polycythaemic hyperviscosity.

Alternatively, not all babies with polycythaemia and hyperviscosity necessarily need to be treated. This issue remains highly controversial and is the problem to which this thesis addresses itself. Weinberger and Oleinick (1971) analysed data from the NIH collaborative study on cerebral palsy. Viscosity studies were not done but babies with Hct values $> 77\%$ were identified and matched with control non-polycythaemic infants. Evaluation of these polycythaemic babies showed a higher incidence of 'placental dysfunction syndrome' abnormalities in the early neonatal period. When tested at 4 years of age the IQ of the polycythaemic babies was not statistically different from the controls. They conclude that the risk from these high haematocrits at birth is low and infer that treatment with haemodilution is not always necessary.

Høst and Ulrich (1982) also examined the problem of late prognosis in untreated polycythaemic neonates with minor or no clinical signs. A group of 30 babies with Hct $> 65\%$ were prospectively studied and these children were evaluated at 2,5 and 6 years of age. Using the Denver Developmental Screening

Test only one polycythaemic child was found to have a 'questionable' result and this child was assessed as normal at 6 years of age. A questionnaire sent to the children's parents was used for the 6 year assessment. Problems reported included one case each of convulsions, nocturnal enuresis and gross motor clumsiness. The authors conclude that preventative haemodilution was not indicated in the cases of neonatal polycythaemia with minor or no symptoms that they studied.

In conclusion, it would seem reasonable and desirable that babies with severe signs related to neonatal polycythaemic hyperviscosity should be treated using PPET or some form of haemodilution. The management of babies with NPHV but who appear clinically well or have minor signs remains controversial. Further studies are indicated to assess the value of PPET in affected but relatively well babies.

# PART II

# DATA COLLECTION

## CHAPTER 1 : PATIENTS

The study was approved by the Ethics and Research Committee of the Faculty of Medicine of the University of Cape Town. For each baby studied the parent(s) were interviewed and informed consent was obtained.

### 1.1 OBJECTIVES

#### 1.1.1 Method of Sampling

During the period June 1976 to June 1977, when work for this study was done, newborn babies were examined for the presence of polycythaemia and high blood viscosity. These newborns were from parents of mixed race resident in Cape Town (R.S.A.). Each baby studied had an unwarmed and a warmed heelprick Hct plus a cubital vein Hct and venous blood viscosity measured. The time that the umbilical cord was clamped had been controlled and was done early (5-15 sec). Some of the infants were found to be polycythaemic and hyperviscous (see Aim, Section 1.2, pg 52), while others had Hct and viscosity values within the normal range. A total of 87 babies was studied, each having data on peripheral and venous Hct and viscosity. These patient data

were used to examine the relationship between the method of Hct sampling and whole venous blood viscosity.

1.1.2 Normal Viscosity Values

The international literature was reviewed to find normal viscosity values for newborns. Particular care was taken to find data for babies in the early neonatal period and to find data which had been determined using the same methods as in this study.

To determine if babies in this study population had similar viscosity values to those published, ten normal babies were examined at birth and daily for 4 days. These 10 babies had been born following a normal antenatal course, were at term, appropriately grown and clinically well. They were all born electively by Caesarean Section because of previous Caesarean Section. This was the hospital policy at the time. These mothers and babies stay in hospital longer (6-7 days) than those delivered vaginally (24 hours). Informed consent was obtained from the mother in each case. Each baby was examined daily. Umbilical vein blood was collected at birth and venous blood at 12 hours, 2, 3 and 4 days of age. Haematocrit and viscosity determinations were done on each sample.

The values obtained in these 10 normal babies were compared with those of published data. Published data which was similar to that of the local babies was used for normal reference viscosity values. Hyperviscosity was defined as values greater than the normal mean plus 2 standard deviations at each shear rate from 11,5 through 230 $sec^{-1}$.

Having examined the two objectives, which in themselves were prerequisites to the study, the main aim of the work could be addressed.

## 1.2 THE AIM

### 1.2.1 Hyperviscosity Treatment Study (HTS)

The study sample was made up of neonates born to a population of women of mixed race resident in the Cape Peninsula (RSA). These babies were delivered at Groote Schuur Hospital Maternity Centre between June 1976 and June 1977. Babies from this ethnic group represent a significant proportion (71%) of the Cape Town newborn population (de Groote 1977) and for this reason were selected for study. Babies born to both black and white mothers were initially included in the sample but were later excluded. The black children were excluded because the social and political constraints present at the time of study made their follow-up almost impossible. As white babies were delivered and cared for in separate maternity hospitals, they were not readily available for study. Since there was an equal distribution of babies from different racial groups, it was decided that, although not ideal, the study be confined to one group only and for this reason babies born to mothers of mixed race were chosen.

Polycythaemic babies were recruited into the study sample in a non-selected manner. In practice, babies were sequentially recruited as the presence of polycythaemia was recognised.

Babies born during inconvenient hours could not be included. The time of umbilical cord clamping was not controlled but it was not delayed. In a previous study (van der Elst et al 1978) the observed time from the delivery of the baby to clamping of the cord was between 5 and 15 seconds. Study infants were identified if they appeared clinically plethoric. These babies then had an unwarmed heelprick capillary haematocrit (Hct) performed. If this Hct value was $\geqslant$ 65% a warmed heelprick and central cubital vein blood Hct was measured. If the central Hct was $\geqslant$ 65% then viscosity studies were done on the venous blood specimen. If these results were abnormal (see Normal Viscosity Values, Part III Chapter 2, pg 74-80) the baby was recruited for the Hyperviscosity Treatment Study (n = 41). Patients with NPHV were randomly assigned to receive partial plasma exchange transfusion (PPET) or symptomatic and general nursery care only. Random allocation numbers had been obtained from published tables (Diem 1962). One hyperviscous infant with severe hyaline membrane disease was considered too ill to be included in a randomised study.

Another infant with Trisomy 21 was also excluded. Those babies undergoing PPET were identified as Group A (n = 20) while those not exchanged were Group B (n = 21).

In addition, a further group of babies who were neither polycythaemic nor hyperviscous was collected. These control babies were identified as Group C (n = 31) and were matched for gestational age, weight, 5 minute Apgar Score and postnatal age with the Groups A and B. These Group C babies were selected if

their antenatal, intrapartum and subsequent postnatal course had been completely free of problems.

All babies were kept in the same nursery and received the same general nursing care. This consisted of regular 3 hourly feeding or demand breast milk feeds when possible, thermal care, routine bathing, cord care, etc. Except for the Group A babies who received a PPET, the care was the same in all three groups.

The babies and mothers were discharged home once their condition was satisfactory. Babies were examined daily and considered well enough to go home if there were no clinical signs of NPHV.

Regular contact was maintained with as many of the families as possible. Follow-up visits or assessment appointments were made regularly. Prepaid addressed envelopes were issued so that any change of address could be notified. Where domiciliary addresses had changed and no notification received, neighbours and other family members helped in locating the patient. Two patients had left the Cape Peninsula. One was living in Port

Elizabeth (R.S.A.) and the other in Toronto (Canada). The child in Port Elizabeth was flown to Cape Town for testing while the child in Canada was examined by Developmentalists in Toronto.

One infant died (aged 4 months) of gastroenteritis. Therefore, no follow-up data was available for that child.

# CHAPTER 2 : METHODS

All of the blood samples were collected by the author using standard methods. These blood samples were processed in a side room attached to the nursery. Here Hct and whole blood viscosity values were determined.

## 2.1 THE HAEMATOCRIT

The method of obtaining a capillary blood sample for the Hct determination was that described by Hughes and Buescher (1980). The medial aspect of the babies heel was cleaned with an alcohol swab and then pricked with a 3 mm lancet (Feather Blood Lancets). The ankle and foot were then gently squeezed so that a drop of blood appeared at the puncture site. This was then drawn into a capillary tube (1,1 x 75 mm), sealed with plasticine and centrifuged at 12,000 rpm for 5 minutes. The Hct was determined by the height of the column of packed red blood cells expressed as a percentage of the height of the red cells and plasma.

All the babies had a central venous Hct measurement. Blood was drawn from the cubital or, on rare occasions (2 babies), from the external jugular vein. Venipuncture was performed using a 23 gauge needle as described by Hughes and Buescher (1980). A 2 ml sample of blood was taken and gently mixed with 0,05 ml of heparin (25 units/ml) in a glass test tube (Zingg et al 1973). Blood was placed into capillary tubes, sealed at one end with

plasticine and again centrifuged at 12,000 rpm for 5 minutes. The Hct was read in the standard manner.

## 2.2 WHOLE BLOOD VISCOSITY

Whole blood viscosity was measured using a Wells-Brookfield Synchro-Lectric Microviscometer Model LTV. Details of the physical and geometric features of the instrument are described in the Appendix. The measurement of blood viscosity was carried out according to the method described by the manufacturers.

Briefly, 1,2 ml of heparinised whole blood was placed on a stationary plate in the form of a rhodium cup. This cup surrounds the cone of the viscometer. The cup was heated to 37°C by means of a water jacket connected to a hot water bath. The cone was made to rotate in the sample of blood at various speeds (3, 6, 12, 30 and 60 rpm) from which the viscosity at shear rates 11,5, 23, 46, 115 and 230 $sec^{-1}$ respectively were calculated. The drag or SHEAR STRESS on the rotating cone caused by the blood was measured on a dial by means of a calibrated beryllium spring mounted on the drive shaft. Thus the SHEAR STRESS at various SHEAR RATES could be determined and the whole blood viscosity calculated from this data.

At the beginning of the measurement of each sample the instrument was allowed to run at 60 rpm for 5 minutes. This allowed stabilisation of the sample before measurements were made. Following this, an average of 2 dial readings was taken for each speed setting and this value was then multiplied by a given factor (see Appendix) which gave the viscosity of the blood sample at that particular shear rate.

Results of whole blood viscosity were available for all cases studied and hyperviscous babies were identified if their values were greater than the normal data as previously determined.

## 2.3 OBJECTIVES

### 2.3.1 Method of Sampling

Blood samples for this part of the study were drawn either from the heel of the infant or the cubital vein. In each baby studied an unwarmed heelprick capillary Hct was obtained (often with difficulty) according to the method described by Hughes and Beuscher (1980). The medial aspect of the babies' unwarmed heel was pricked with a 3 mm lancet (Feather Blood Lancets). Blood was squeezed as gently as possible from the puncture site and allowed to flow into capillary tubes.

The opposite foot was then warmed in a bath of water at 40°C for 5 minutes (Oh et al, 1966). Once hyperaemia had occurred, a warmed heelprick Hct was performed. At approximately the same time a cubital vein sample representing central venous blood was obtained for Hct and viscosity studies. The results of the unwarmed, the warmed heelprick Hct and the central venous Hct were compared and correlated with the whole blood viscosity values.

### 2.3.2 Normal Viscosity Values

In each of the 10 cases studied informed consent was obtained from the parents before sampling commenced. At birth 2 ml of

umbilical cord venous blood was taken and mixed with 0,05 ml of heparin (25 units/ml). Blood was then taken from the cubital vein at 12 hours, on days 2, 3 and 4, heparinised and tested. For each sample a Hct and whole blood viscosity was done.

Each baby was examined clinically at birth and again on each day of the study. The babies all received formula milk (60 ml/kg/day) on day 1 as this was the policy in the nursery at that time. Thereafter, the babies were breast fed for the rest of the study period.

## 2.4 THE HYPERVISCOSITY TREATMENT STUDY

### 2.4.1 Clinical Data

All babies who had been identified as being hyperviscous (Groups A and B) or as control infants (Group C) were examined clinically and investigated further. The post delivery age of the baby, the gestational age (Dubowitz et al 1970), weight, length, head circumference, Apgar score and sex of the infant were recorded. The anthropometric measurements were plotted on percentile graphs (NCHS 1976) and note was made of measurements where the plot was above the 90th or below the 10th percentiles.

Babies were examined for clinical signs and in particular for those clinical signs which may have resulted from the presence of hyperviscosity in the infant. Clinical signs were divided into two categories. Those that were thought to be of a less serious nature were called MINOR signs while the more serious

signs were designated MAJOR. Although the selection of signs was done by the author using his own clinical judgement it is important to note that the classification was arbitrarily done and did not necessarily represent an accepted grading of polycythaemia and hyperviscosity. This division of signs was thought to be clinically logical as it was presumed that signs classified as MAJOR would be more likely to affect the long-term outcome in these infants. The aim of the study was to evaluate the benefit of PPET in NPHV babies with MINOR or with no apparent clinical signs. This division of clinical signs was thus necessary.

SIGNS OF NEONATAL HYPERVISCOSITY

| MINOR | MAJOR |
|---|---|
| Peripheral cyanosis | Central cyanosis |
| Tremulousness | Respiratory distress |
| Lethargy | Apnoea |
| Hypotonia | Convulsions |
| Irritability | Hypoglycaemia |
| Poor feeding | |
| Vomiting | |

### 2.4.2 Investigations

Each of the hyperviscous babies had a chest radiograph, an electrocardiogram, and a plasma calcium and magnesium estimation done. The plasma calcium and magnesium levels were done in order to exclude low levels as a cause for signs such as

tremulousness and convulsions. Regular blood glucose (Dextrostix, Aims) determinations were done during the first few days of life.

2.4.3 Partial Plasma Exchange Transfusion

Having randomised the hyperviscous babies, partial plasma exchange tranfusion was performed in Group A babies as soon as possible after the diagnosis was made. Catheterisation of the umbilical vein was done as described by Hughes and Buescher (1980). A polyvinyl catheter was inserted into the inferior vena cava via the umbilical vein and ductus venosus under radiographic control (Baker et al 1969). The volume which was exchanged in each baby was calculated from the formula:

Volume of exchange (ml) =

$$\frac{\text{Weight (kg)} \times 90 \text{ ml/kg} \times (\text{Observed Hct} - 60)}{\text{Observed Hct}}$$ (Phibbs 1977)

The exchange transfusion was performed in aliquots of 5-10 ml until the calculated volume of previously warmed fresh frozen plasma had been exchanged. Blood haematocrit and viscosity studies were repeated immediately after the exchange, to ensure that they were within the normal range. One patient required a repeat exchange transfusion after 48 hours as the blood viscosity had again increased to above normal values.

Babies in Groups A, B and C were all examined daily until discharged home. They also had daily Hct determinations done during this period. This was done in order to monitor the Hct status of the babies in the 3 groups.

2.4.4 Neurobehavioural Testing

At approximately 1 to 2 weeks of age each baby was examined by the author using a Neonatal Behavioural Assessment Scale (NBAS) (Brazelton 1973) and a Neurological Assessment (Prechtl 1975). The examination was carried out according to the recommendations and specifications of the authors of each test. Specifically, infants were tested in a quiet room with subdued lights at approximately 1 hour before a feed and using the standard equipment recommended. Babies were scored according to their best performance.

2.4.5 Follow-Up

The infants were seen again at 32 weeks of age when neurological and developmental assessments were done. The examiner (a paediatric neurologist), had no prior knowledge of the Group assignment so that the examination was done without any known bias.

The neurological assessment done was a general test of central nervous system function. It included assessment of muscle tone and power, sensation, coordination, tendon reflexes and cranial nerve function. The developmental scale used was that devised by the Developmental Clinic at the Red Cross War Memorial Children's Hospital, Cape Town. The scale was similar to the Griffiths Developmental Score (Griffiths 1954) in many respects. The child was tested according to various abilities expected at that age and a total score given in each case. The expected average score for 32 week old children would be $102 \pm 11{,}35$. A correction for preterm gestation was made where necessary.

The children were assessed again at 24 months of age when a Denver Developmental Screening Test (Frankenberg et al 1971) was done by the author. The assessment was done in each child's home and in each case the child's best performance was scored. The data was recorded and analysed according to standard recommendations.

The final assessment was done by a paediatric neurologist and a clinical psychologist when the children reached the school going age of 6-7 years. At this time data was collected of their actual age, weight, height and head circumference. These were plotted on percentile graphs (NCHS 1976, Nellhaus 1968). The educational status (i.e. highest school standard achieved) was recorded for both the mother and father of each child.

The neurological, visual perception and intelligence testing of these children was done by an experienced neurologist and by a psychologist. The examiners were not aware of the original neonatal Group allocation.

The neurological testing was done according to the examination of Touwen and Prechtl (1970). This test is designed to detect minor nervous dysfunction. The results of the tests were assessed such that a score of 0 would be optimal but a score of $< 19$ would be acceptable for children aged 6-7 years.

The method of scoring the child's performance using an optimal score rating is recommended by the authors of the test.

The visual perception of the children was assessed by applying the Marianne Frostig Developmental Test of Visual Perception (Frostig et al 1964(a)). This test identifies children with problems of hand-eye coordination, figure-ground perception, form constancy, position in space and spatial relationships. The test was first constructed in 1958 and was finally standardised in 1963 (Frostig et al 1964(b)). The test is appropriate for use in children between the ages of 3 and 9 years.

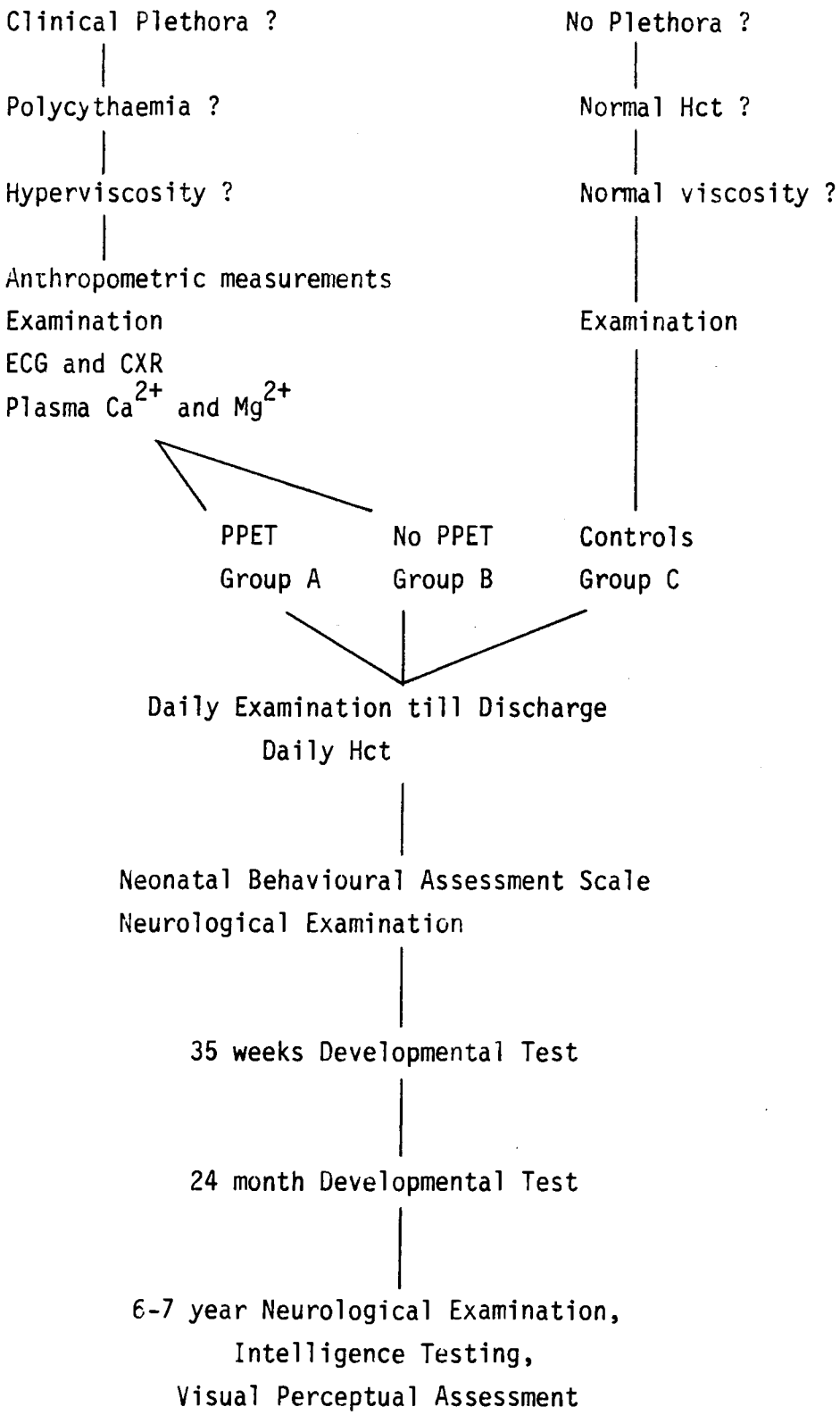
Testing of intelligence was done by applying the new South African Individual Scale (Madge and Van der Westhuizen 1971). The scale measures intellectual behaviour by testing the child's comprehension, vocabulary, verbal reasoning, problem solving ability, memory, pattern completion ability, ability to identify absurdities and ability to work with a form board. The test has been standardised and is appropriate for both English and Afrikaans speaking school-going children. The raw scores for each test administered are converted to a scaled score according to the child's age. This scaled score is converted into an Intelligence Quotient (IQ). The result is given as a Verbal IQ, a non-Verbal IQ and a Full Scale IQ (the sum of the Verbal and non-Verbal IQ's).

These three tests were done in the case of each child over a 2 hour period and not more than 3 children were tested on any one day.

A summary of the clinical methods used in the Hyperviscosity Treatment Study is shown in Figure 2.1

FIGURE 2.1

PLAN OF CLINICAL METHODS



# CHAPTER 3 : METHOD OF DATA COLLECTION AND ANALYSIS

All data were recorded on data sheets and filed under the child's name and identity code. Details were added to these files over the years as the results became available. The final analysis was done with the aid of both calculators and computers. Standard statistical methods were used for the analysis and these were kept as simple as possible.

Parametric data included means, standard deviations, ranges, two tailed t tests, paired t tests and analyses of variance. Non-parametric tests were the Mann-Whitney u test, Chi square ($x^2$) and Fisher's Exact test of probability. A correlation matrix of variables was constructed. Linear relationships between variables were derived where appropriate.

The Bonferroni Inequality (Ingelfinger 1983) which states that, when 2 or more samples are compared with a single control sample, the significance of the p value must be adjusted. In this study, some latitude was considered acceptable in the interpretation of statistical results applied to biological subjects. Significance was accepted at the 5% level ($p = < 0,05$).

# PART III

# RESULTS

## CHAPTER 1 : METHOD OF SAMPLING

Eighty seven babies were studied. Each had an unwarmed heelprick, a warmed heelprick and a central venous Hct done at the same time.

### 1.1 HAEMATOCRIT (%)

The results of the 3 different methods of sampling are shown in Table 1.1. Warming the heel before blood sampling results in a Hct value which approximates the central venous value.

Table 1.2 shows the results (p value) of the paired t test done on these variables. In each comparison there was a highly significant difference. This difference between the warmed heel prick Hct and the central venous value is statistically significant but no biological explanation is tendered.

When the difference between the unwarmed heelprick Hct and the central venous value was calculated for each of the 87 babies sampled, the mean difference was 11,5%, SD 18,3%. The range of differences was from 26% to -7%. Two babies had unwarmed heelprick Hct values which were lower than the central venous value.

TABLE 1.1

METHOD OF SAMPLING: HAEMATOCRIT (%) VALUES OF SAMPLES OBTAINED FROM 3 SITES

| SITE | MEAN | SD | MINIMUM | MAXIMUM |
|---|---|---|---|---|
| Unwarmed heel | 63,9 | 12,0 | 44 | 88 |
| Warmed heel | 56,4 | 8,8 | 41 | 81 |
| Central venous | 54,4 | 8,6 | 37 | 80 |

TABLE 1.2

PAIRED t TEST BETWEEN THE Hct VALUES OBTAINED FROM THE 3 METHODS OF TESTING

| SITES COMPARED | p VALUE |
|---|---|
| Unwarmed heel/warmed heel | $< 0,001$ |
| Unwarmed heel/central venous | $< 0,001$ |
| Warmed heel/central venous | $< 0,001$ |

TABLE 1.3

REGRESSION ANALYSIS (r = CORRELATION COEFFICIENT) BETWEEN 3 METHODS OF Hct BLOOD SAMPLING

| SITES COMPARED | r | p VALUE |
|---|---|---|
| Unwarmed heel/warmed heel | 0,78 | $< 0,001$ |
| Unwarmed heel/central venous | 0,78 | $< 0,001$ |
| Warmed heel /central venous | 0,95 | $< 0,001$ |

Warming the heel improved this heelprick capillary Hct difference to a mean of 2%, SD 2,7%. The range between the warmed heel value and the central Hct was 8% to -4%. Again there were instances (15 cases) where the warmed heel Hct value was lower than the central value.

Regression analysis was also done to observe the relationship between methods of sampling (Table 1.3). In each comparison a highly significant r value was obtained but the best correlation was between the warmed and the central venous Hct values. The regression lines are shown in Figure 1.1, 1.2 and 1.3. These scattergrams demonstrate the dispersion (SD) of results about the regression line. Values tend to cluster closer to the line when the warmed heelprick and the central venous values are compared. The dashed lines represent the 99% confidence limits that a second regression analysis line for the same population, but a different sample, would fall between.

## 1.2 METHOD OF Hct SAMPLING AND WHOLE BLOOD VISCOSITY

The relationships between the various methods of blood sample collection for Hct, the presence of NP (Hct $\geqslant$ 65%) and the actual blood viscosity as determined from central venous blood, were examined. The upper limits of normal blood viscosity were taken from the results (mean + 2 SD) of the 10 Normal babies studied and reported in Part III, Results, Chapter 2, pg 74-79). For each method of Hct sampling the sensitivity, specificity, positive predictive accuracy and negative predictive accuracy (Galen and Gambino 1977) (see Definitions) for the presence of hyperviscosity, are shown in Table 1.4. The sensitivity of Hct

TABLE 1.4

METHOD OF SAMPLING: SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE ACCURACY AND NEGATIVE PREDICTIVE ACCURACY BETWEEN Hct $\geqslant$ 65% AND HYPERVISCOSITY

| | UNWARMED HEEL Hct $\geqslant$ 65% | WARMED HEEL Hct $\geqslant$ 65% | CENTRAL VENOUS Hct $\geqslant$ 65% |
|---|---|---|---|
| Sensitivity % | 100 | 100 | 91 |
| Specificity % | 59 | 93,4 | 98,7 |
| Positive predictability % | 26,2 | 68 | 91 |
| Negative predictability % | 100 | 100 | 98,7 |

FIGURE 1.1

METHOD OF SAMPLING - REGRESSION ANALYSIS - UNWARMED vs WARMED Hct

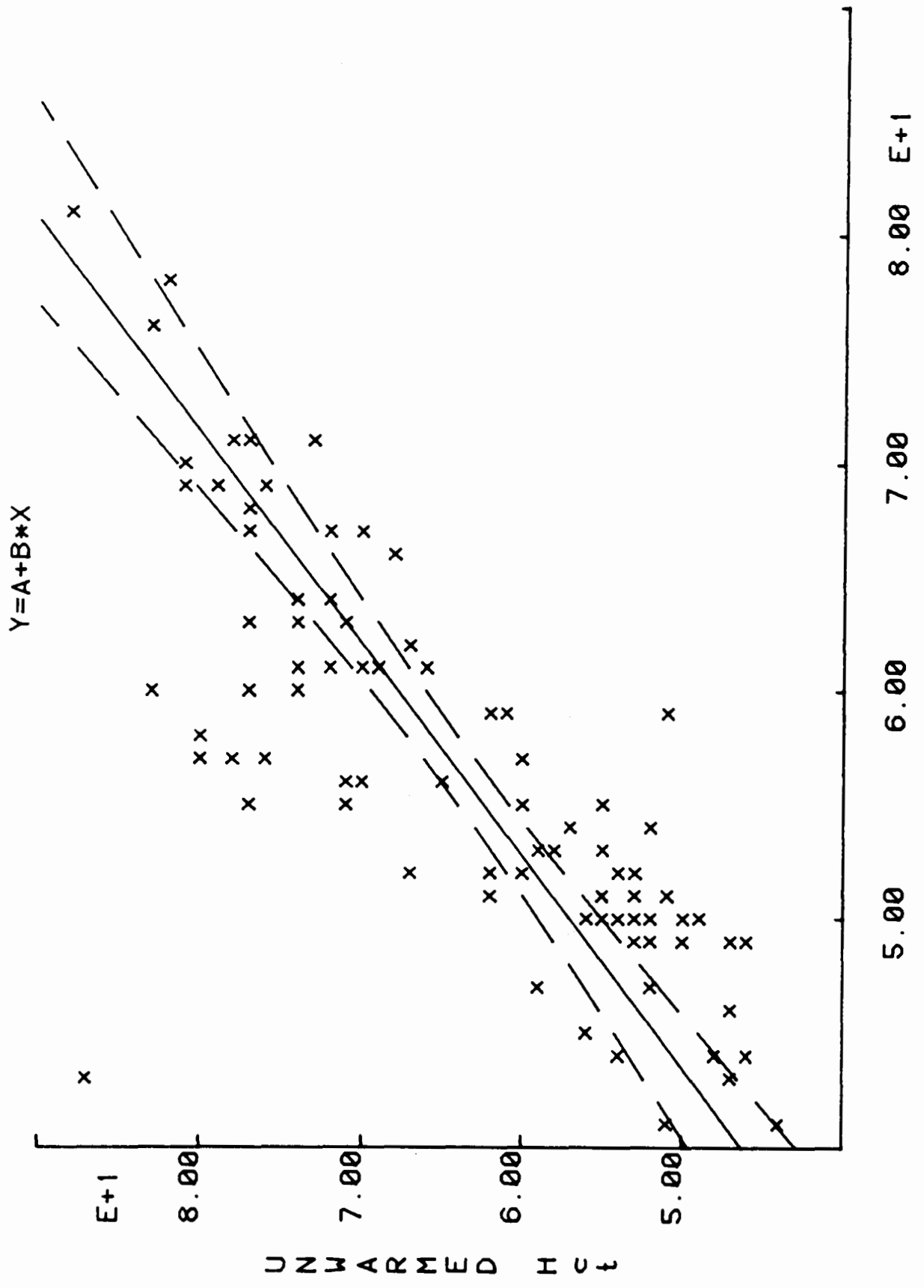


FIGURE 1.2

METHOD OF SAMPLING - REGRESSION ANALYSIS - UNWARMED AND CENTRAL Hct

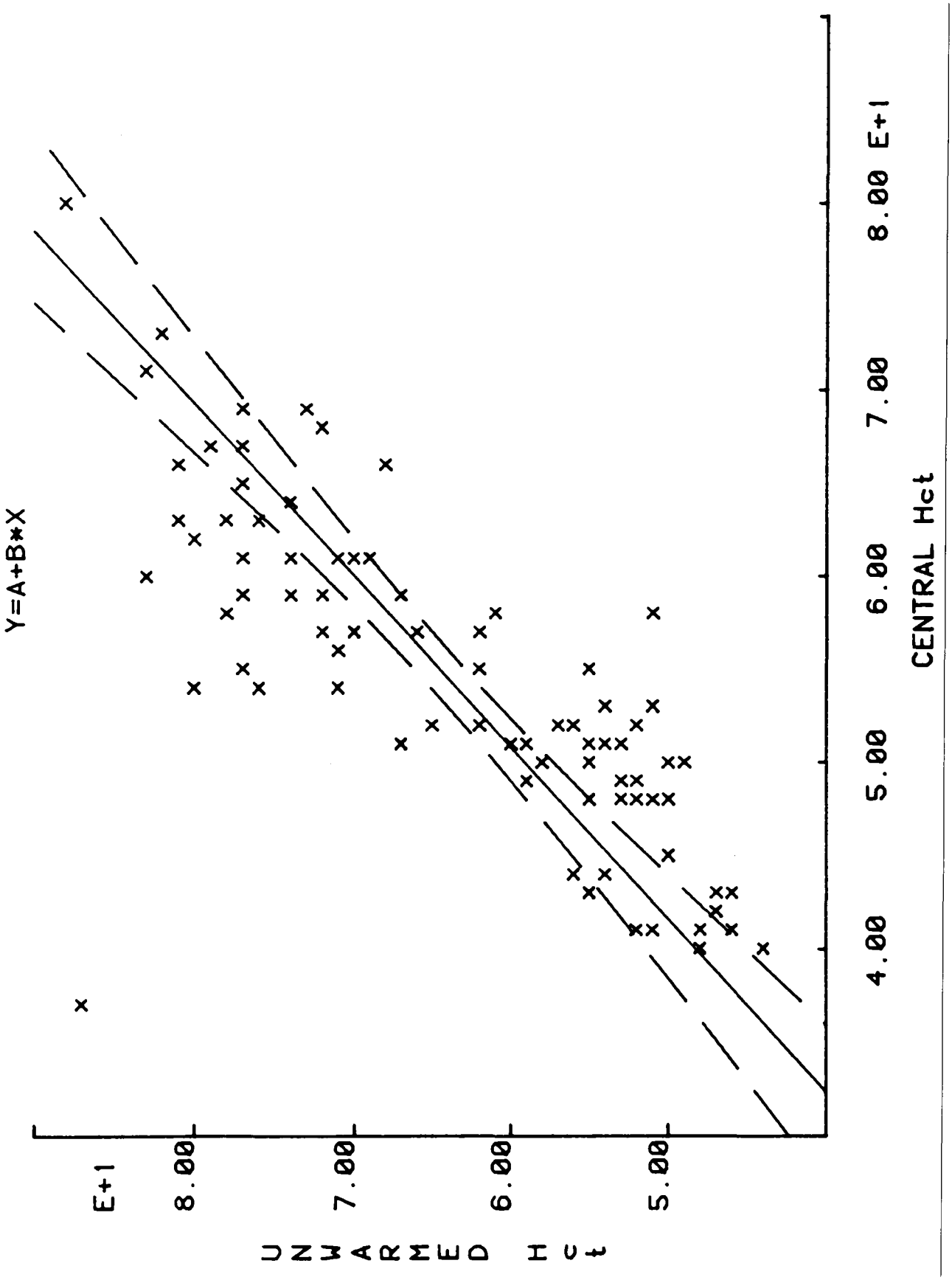
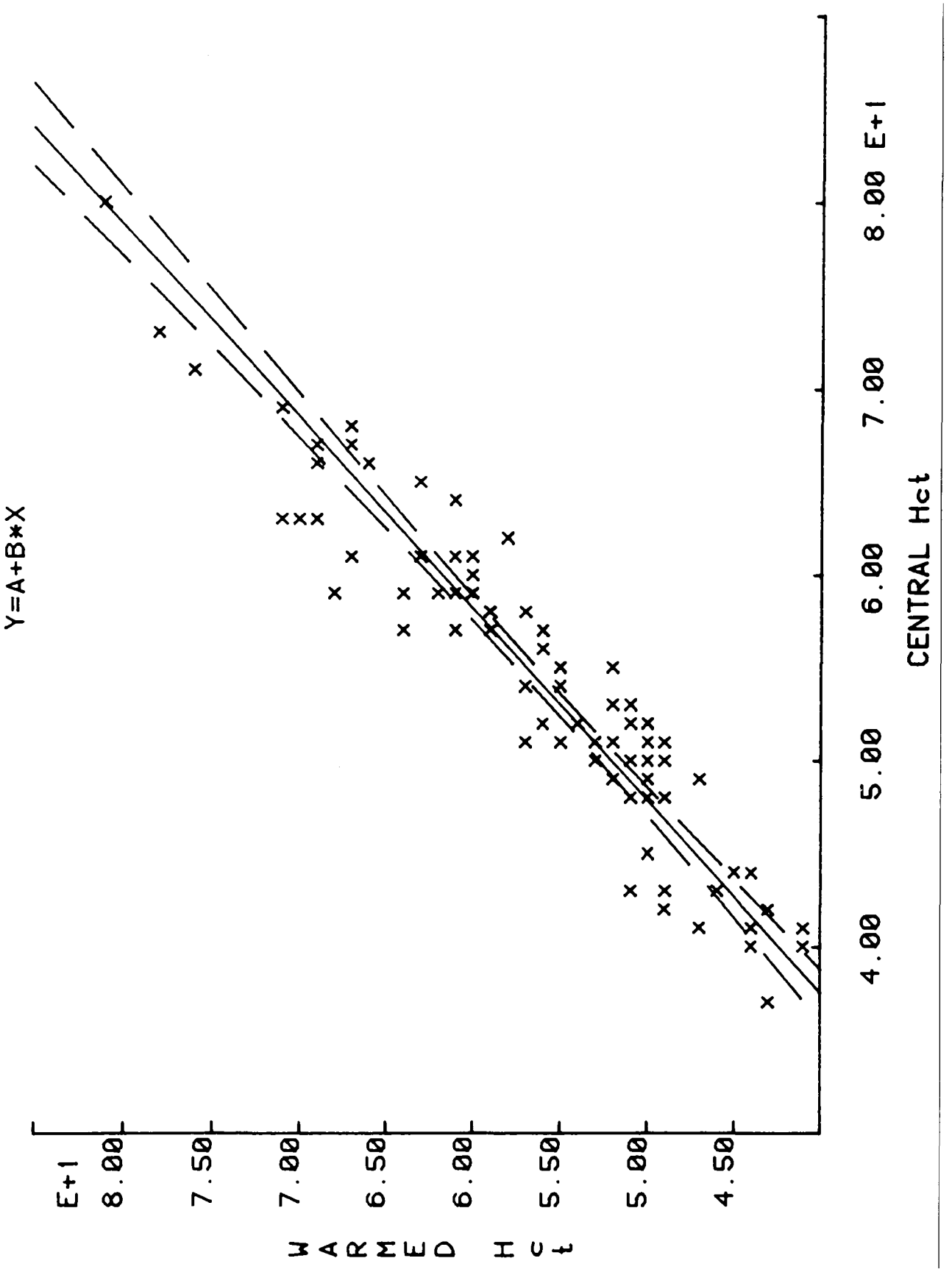


FIGURE 1.3

METHOD OF SAMPLING - REGRESSION ANALYSIS - WARMED vs CENTRAL Hct



sampling was found to be high for all these methods. Warming the heel improved the specificity. The positive predictive accuracy was improved from 26,2% to 68% by warming the heel and was very high for central venous blood samples (91%). The negative predictive accuracy was high for all methods of Hct sampling.

None of the heel-prick Hct values (warmed or unwarmed heel) $\leq$ 65% were found to be from hyperviscous infants. One infant, however, with a cubital vein Hct of 63% was hyperviscous.

The results show that in a NPHV baby warming the heel before Hct sampling is done greatly improves the prediction of abnormality in that infant.

# CHAPTER 2 : NORMAL VISCOSITY VALUES

## 2.1 LITERATURE REVIEW

A review of the literature revealed 5 publications on normal viscosity data for the newborn. Results from these papers are shown in Figure 2.1 There was considerable disagreement as to what were normal viscosity values. Some of the mean values published were more than twice those of other authors. Most articles gave mean values $\pm$ 1 SD and not 2 SD. The normal data of Bergqvist (1973) and of Sommer (1971) could be considered to be in the hyperviscous range. A further study by Shohat et al (1984(b)) examined normal viscosity during the first 12-18 hours of life. Their figures show a considerable variation in the normal viscosity values over this period.

## 2.2 NORMAL VISCOSITY VALUES

The 10 normal babies studied in this thesis from birth to 4 days of age were all at term, the mean birth weight was 3369 g ($\pm$ 413 g) and all were healthy babies. Results of their viscosity determinations are shown in Table 2.1 and in Figure 2.2. The corresponding Hct values at birth and on the subsequent 4 days are shown Table 2.2 and in Figure 2.3. There are highly significant differences ($p = < 0,001$) between Hct values on cord blood and at 12 hours, 12 hours and Day 2, Day 2 and Day 3, Day 3 and Day 4.

FIGURE 2.1

A COMPARISON OF NORMAL WHOLE BLOOD VISCOSITY (cps) VALUES AT DIFFERENT SHEAR RATES AS PUBLISHED BY 5 AUTHORS

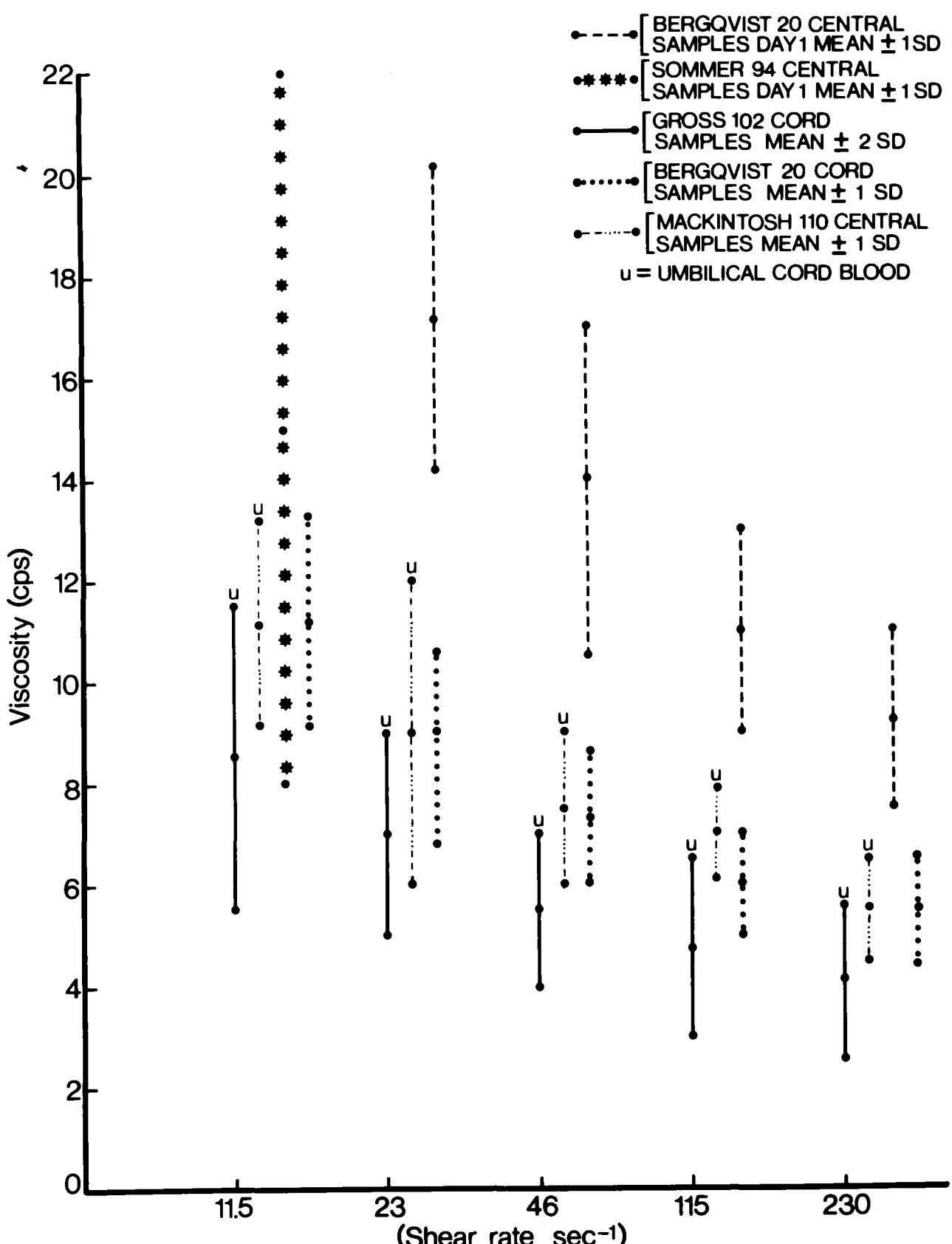


TABLE 2.1

VISCOSITY AT VARYING SHEAR RATES IN 10 NORMAL BABIES

(Mean ± 2 SD)

| SAMPLE TIME | n | SHEAR RATE ($sec^{-1}$) | | | | |
|---|---|---|---|---|---|---|
| | | 11,5 | 23 | 46 | 115 | 230 |
| Birth (Cord) | 10 | 7,72 ± 3,3 | 6,03 ± 2,12 | 5,03 ± 1,63 | 4,14 ± 1,24 | 3,78 ± 1,2 |
| 12 hours | 9 | 9,73 ± 4,98 | 7,82 ± 3,74 | 6,43 ± 2,74 | 5,25 ± 2,08 | 4,82 ± 2,08 |
| 24-48 hours | 10 | 9,41 ± 4,12 | 7,49 ± 2,66 | 6,01 ± 1,96 | 4,92 ± 1,52 | 4,36 ± 1,38 |
| 48-72 hours | 10 | 9,0 ± 3,32 | 7,14 ± 2,26 | 5,85 ± 1,56 | 4,70 ± 1,2 | 4,25 ± 1,06 |
| 72-96 hours | 9 | 9,19 ± 2,70 | 7,49 ± 1,84 | 6,13 ± 1,16 | 4,93 ± 0,88 | 4,38 ± 0,82 |

FIGURE 2.2

BLOOD VISCOSITY AT VARYING SHEAR RATES IN 10 NORMAL BABIES FROM BIRTH TO 4 DAYS OF AGE (Mean ± 2 SD)

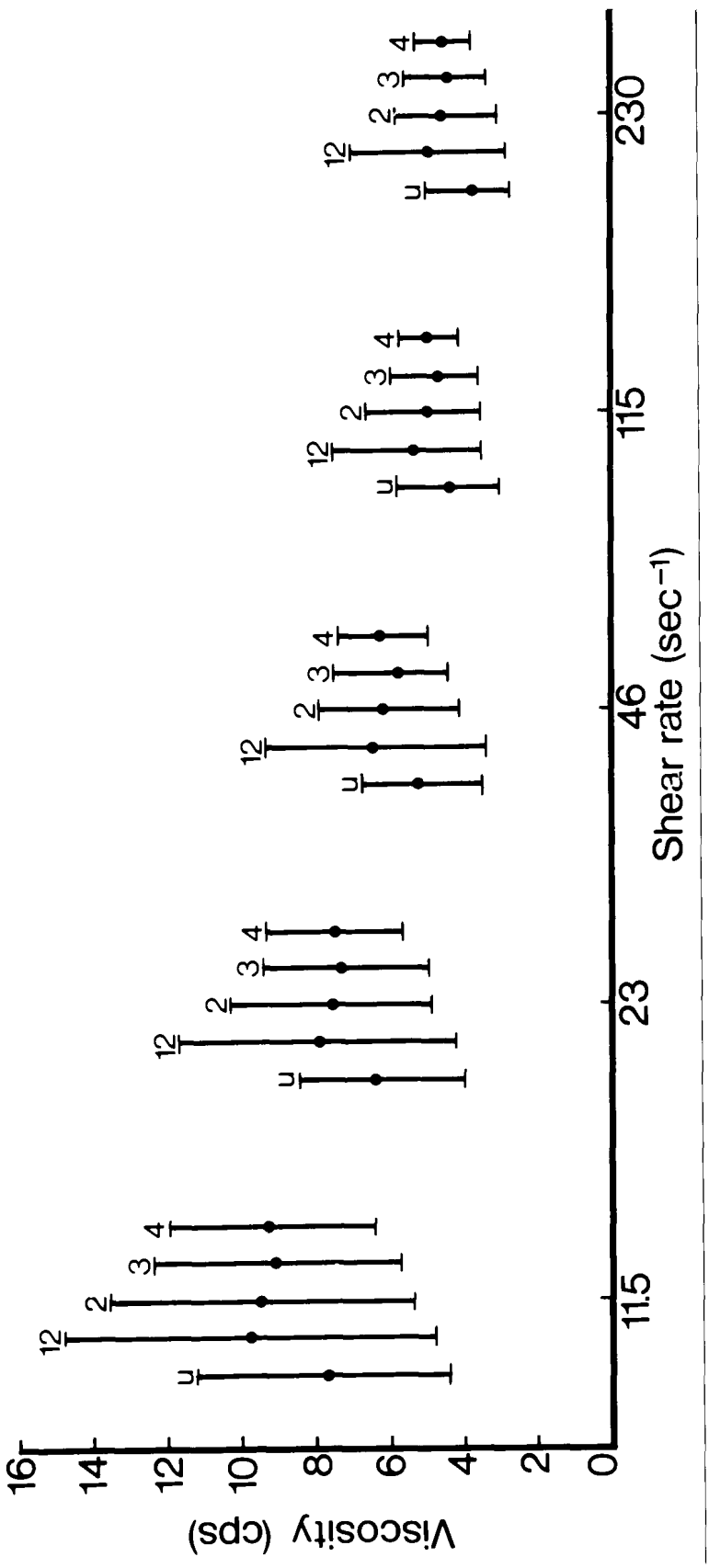


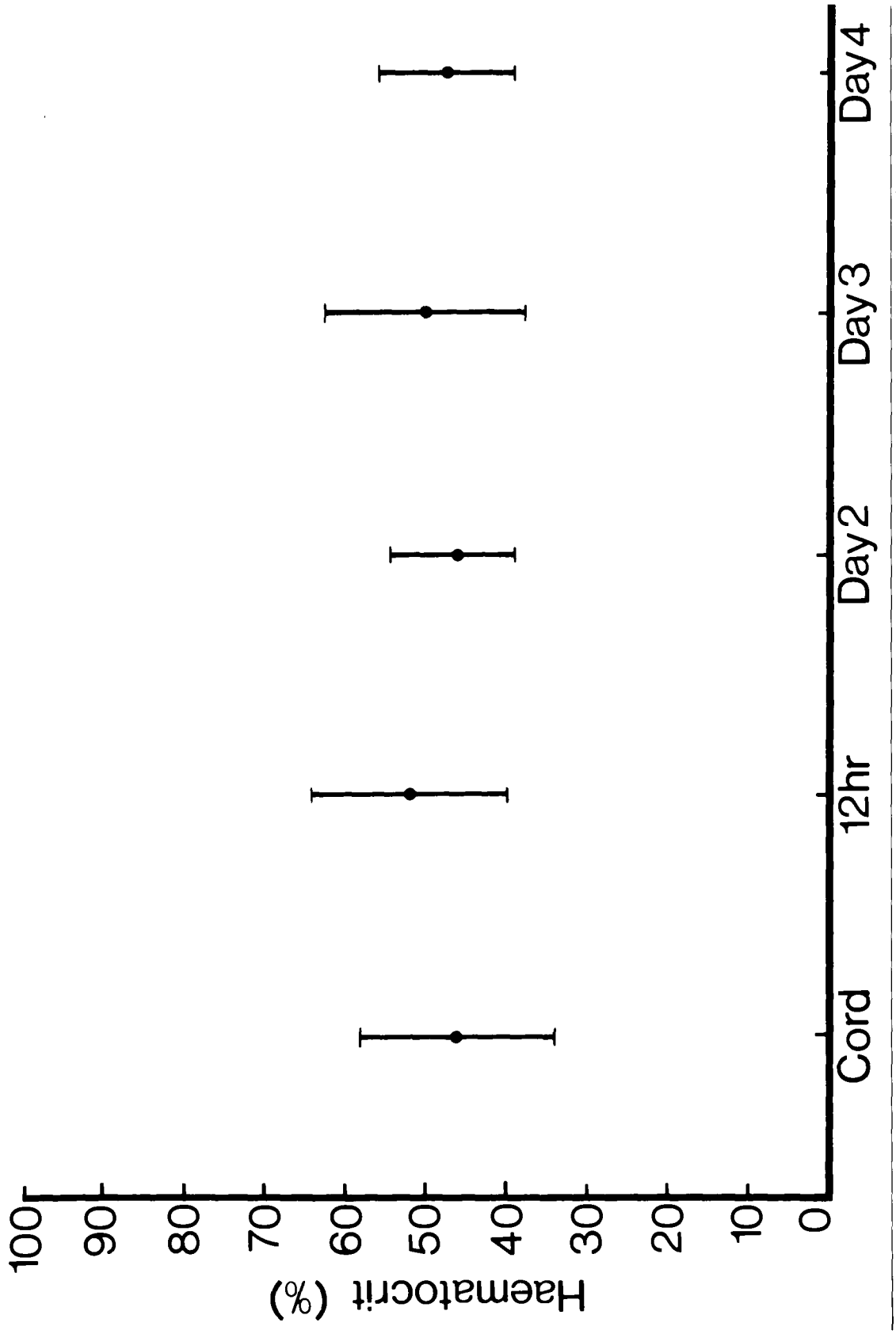
TABLE 2.2

VENOUS HAEMATOCRIT VALUES IN 10 NORMAL BABIES FROM BIRTH TO 4 DAYS OF AGE : COMPARISON BETWEEN THE TIMES

| SAMPLE TIME | VENOUS Hct % (mean $\pm$ 2 SD) | p VALUE COMPARISON BETWEEN TIMES |
|---|---|---|
| Cord Blood | 46,2 $\pm$ 12,1 | |
| | | < 0,001 |
| 12 Hours | 52,2 $\pm$ 12,2 | |
| | | < 0,001 |
| Day 2 | 46,8 $\pm$ 7,8 | |
| | | < 0,001 |
| Day 3 | 50 $\pm$ 12,4 | |
| | | <0,001 |
| Day 4 | 47,1 $\pm$ 8,2 | |

FIGURE 2.3

VENOUS HAEMATOCRIT VALUES IN 10 NORMAL BABIES FROM BIRTH TO 4 DAYS OF AGE (Mean ± 2 SD)



Comparisons of this study with published data of normal values showed that the values of Gross et al (1973) (cord blood) and those of Mackintosh and Walker (1973) (Day 1) were acceptable as normal reference values. Thus hyperviscous babies in this study were selected if their viscosity levels were above those considered normal by the above two authors. In addition, the study babies' viscosity levels were above those of the 10 normal babies studied in this thesis. Due regard was taken of the age of the baby from birth in deciding if the study babies were hyperviscous. None of the Group A or B babies had viscosities in excess of those in the control group, Group C (see page 86).

# CHAPTER 3 : HYPERVISCOUS TREATMENT STUDY

## 3.1 INTRODUCTION

The aim of this part of the study is to evaluate the effects of treatment in hyperviscous neonates. Data relevant to this purpose are presented in this section: firstly for the neonatal period and then for the follow-up period.

### SAMPLE SIZE (n)

The number of babies recruited for the Hyperviscous Treatment Study were:

Hyperviscous Babies : n = 41
- Treated with PPET: n = 20 — Group A
- Not treated with PPET: n = 21 — Group B

Control (normal blood viscosity) babies: n = 31 — Group C

## 3.2 NEONATAL PERIOD

### 3.2.1 Haematocrit (%)

The mean $\pm$SD central venous Hct (%) for the groups are shown in Table 3.1. Babies in Group A before PPET and those in Group B are polycythaemic (Hct $\geq$ 65%). The babies in Group A after

PPET and those in Group C have Hct values within the normal range of 65%.

TABLE 3.1

CENTRAL VENOUS HAEMATOCRIT (%) AT THE BEGINNING OF THE STUDY

| | n | MEAN | S.D. |
|---|---|---|---|
| Group A before PPET | 20 | 70 | 4,5 |
| Group A after PPET | 20 | 47,1 | 4 |
| Group B | 21 | 68,1 | 3 |
| Group C | 31 | 48,9 | 4,7 |

Comparisons between the groups are shown in Table 3.2. There is no significant difference (p = 0,17) between the Hct values of Group A before PPET and those of Group B. The Hct values in Group A after PPET are significantly different (p = 0,001) from Group B but not from Group C (p = 0,09). The Hct values of the Group B babies are significantly different from Group C (p = 0,001).

The mean $\pm$ SD Hct values of the babies in Groups A and B on the subsequent 5 days are shown in Table 3.3. Babies in Group A after PPET have values 65% for the period while most Group B babies remain polycythaemic.

TABLE 3.2

CENTRAL VENOUS HAEMATOCRIT (%) AT THE BEGINNING OF THE STUDY: COMPARISONS BETWEEN THE GROUPS

| | n | p values |
|---|---|---|
| Group A before PPET / Group B | 20/21 | 0,17 |
| Group A after PPET / Group B | 20/21 | <0,001 |
| Group A after PPET / Group C | 20/31 | 0,09 |
| Group B / Group C | 21/32 | <0,001 |

TABLE 3.3

HAEMATOCRIT (%) VALUES (MEAN $\pm$ SD) ON SUBSEQUENT DAYS FOLLOWING ENTRY TO THE STUDY

| | DAY2 | DAY 3 | DAY 4 | DAY 5 |
|---|---|---|---|---|
| Group A after PPET | 60 $\pm$ 4,4 | 57 $\pm$ 4,6 | 56 $\pm$ 6,1 | 55 $\pm$ 5,4 |
| Group B | 70 $\pm$ 5,5 | 69 $\pm$ 6,5 | 67 $\pm$ 5,4 | 67 $\pm$ 5,7 |

### 3.2.2 Whole Blood Viscosity (cps)

The mean $\pm$SD values for whole blood viscosity (cps) at shear rates 11,5 through 230 $sec^{-1}$ for the groups are shown in Table 3.4 In all groups the progressive fall in blood viscosity with increasing shear rate is evident. The viscosity values at all shear rates tested in Group A before PPET and Group B are abnormal when compared with the mean + 2 SD values of Group C (Figure 3.1 and 3.2). Group C viscosity values are similar to the normal blood values (see Part III, Chapter 2, Normal Viscosity Values, pg 74-80). The blood viscosity results of Group A babies after PPET are reduced and similar to group C.

Comparisons of blood viscosity values (t Test) amongst the groups is shown in Table 3.5 There is no difference between the viscosity results of babies in Group A before PPET and group B at any of the shear rates tested. After treatment with PPET, Group A figures are significantly different from Group B but not from Groups C. Group B babies have blood viscosity values which are significantly different from Group C.

### 3.2.3 Anthropometry of the Groups

The results (mean $\pm$SD) of measurements of gestational age (weeks), weight (g), length (cm) and head circumference (cm) are shown in Table 3.6. With regard to gestational age there were 4 preterm ( $<$ 37 completed weeks) babies in Group A, 3 in Group B and 7 matched babies in Group C. No infants were post-term.

TABLE 3.4

WHOLE BLOOD VISCOSITY (cps) MEAN ± S.D. FOR THE GROUPS

Shear rate ($sec^{-1}$)

| | n | 11,5 | 23 | 46 | 115 | 230 |
|---|---|---|---|---|---|---|
| Group A before PPET | 20 | 18,3 ±3,1 | 14 ±2,6 | 13,3±2 | 9 ±1,4 | 8 ±1,1 |
| Group A after PPET | 20 | 9,4 ±1,8 | 9,3±1,2 | 5,7±0,8 | 4,6±0,5 | 4,1±0,6 |
| Group B | 21 | 17,18±2,8 | 13,4±2 | 10,6±1,6 | 8,7±1,2 | 7,7±1 |
| Group C | 31 | 8,7 ±1,9 | 7 ±1,3 | 5,6±0,8 | 4,6±0,7 | 4,2±0,7 |

FIGURE 3.1

WHOLE BLOOD VISCOSITY (cps) OF GROUP C (Mean ± 2 SD) AND INDIVIDUAL VALUES OF GROUP A PRE PPET

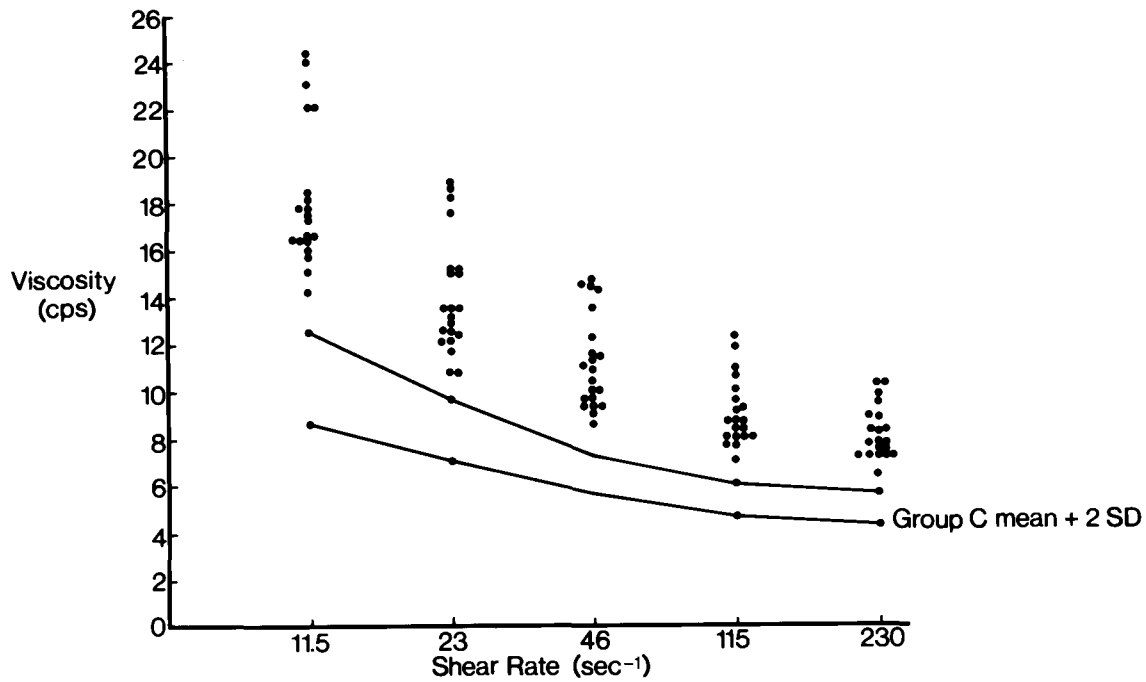



FIGURE 3.2

WHOLE BLOOD VISCOSITY (cps) OF GROUP C (Mean ± 2 SD) AND INDIVIDUAL VALUES OF GROUP B

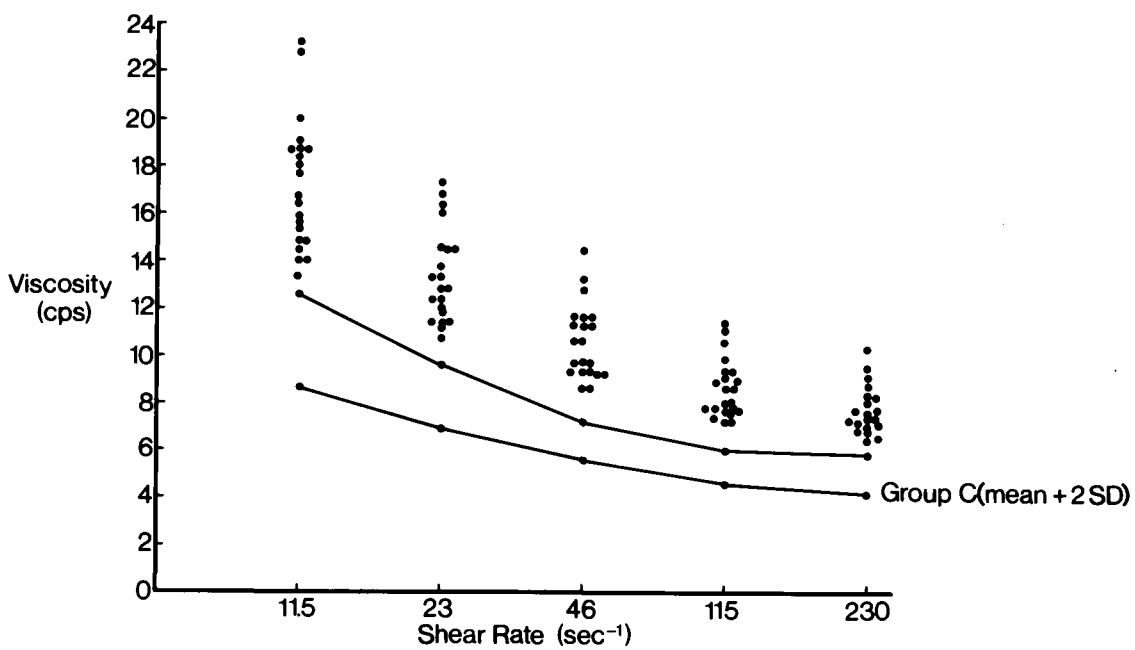


TABLE 3.5

WHOLE BLOOD VISCOSITY (cps) : COMPARISON USING t TEST (p VALUES) OF THE GROUPS

Shear Rate ($sec^{-1}$)

| | 11,5 | 23 | 46 | 115 | 230 |
|---|---|---|---|---|---|
| Group A before PPET/Group B | 0,23 | 0,4 | 0,26 | 0,44 | 0,4 |
| Group A after PPET/Group B | $<$ 0,001 | $<$ 0,001 | $<$ 0,001 | $<$ 0,001 | $<$ 0,001 |
| Group A after PPET/Group C | 0,17 | 0,35 | 0,8 | 0,99 | 0,87 |
| Group B/Group C | $<$ 0,001 | $<$ 0,001 | $<$ 0,001 | $<$ 0,001 | $<$ 0,001 |

TABLE 3.6

ANTHROPOMETRY: MEAN $\pm$ SD VALUES FOR THE GROUPS

| | n | GESTATIONAL AGE (weeks) | WEIGHT (g) | LENGTH (cm) | HEAD CIRCUMFERENCE (cm) |
|---|---|---|---|---|---|
| Group A | 20 | 37,5 $\pm$ 2,8 | 2764 $\pm$ 890 | 47,5 $\pm$ 4,1 | 32,8 $\pm$ 2,6 |
| Group B | 21 | 37,9 $\pm$ 1,5 | 2533 $\pm$ 682 | 46,8 $\pm$ 2,8 | 32,6 $\pm$ 1,8 |
| Group C | 31 | 37,7 $\pm$ 2,2 | 2759 $\pm$ 616 | 47,9 $\pm$ 3,3 | 33,2 $\pm$ 2,2 |

Several babies were underweight. Eight infants in Group A, 13 in Group B and 7 in Group C had birth weights < 2500 g. Two infants in Group A, 9 in Group B (a total of 11 = 27% of the NPHV infants) and 2 in Group C had birthweights below the 10th percentile for gestational age (NCHS 1976). These neonates were small for gestational age. Further analysis of the outcome of these SGA babies was done at 6-7 years of age (see later Table 3.44). Two neonates in Group A and 1 in Group B had weights > 90th percentile (large for gestational age).

There were 8 babies whose length was < 10th percentile (NCHS 1976), 2 were in Group A, 5 in Group B and 1 in Group C.

When head circumference was examined 1 Group A, 3 Group B and 2 Group C babies had measurements < 10th percentile (NCHS 1976). None of these infants were truly microcephalic as other body measurements were similarly deviant and below the 10th percentile.

Table 3.7 shows comparisons (unpaired t test) of the measurements between the groups. There are no significant differences between any of the anthropometric measurements. The groups are thus comparable in this regard.

### 3.2.4 The Sex of the Infants

The distribution of type of sex amongst the groups is shown in Table 3.8. Comparisons (Chi squared test) between the groups is not significant (p = 0,37) but there were 10 more females than males in the entire study sample.

TABLE 3.7

ANTHROPOMETRY: COMPARISONS (p VALUES) BETWEEN THE GROUPS

| | GESTATIONAL AGE (weeks) | WEIGHT (g) | LENGTH (cm) | HEAD CIRCUMFERENCE (cm) |
|---|---|---|---|---|
| Group A / Group B | 0,57 | 0,35 | 0,49 | 0,76 |
| Group A / Group C | 0,84 | 0,97 | 0,76 | 0,61 |
| Group B / Group C | 0,65 | 0,22 | 0,23 | 0,34 |

TABLE 3.8

THE SEX OF THE INFANTS

| | n | MALE | FEMALE |
|---|---|---|---|
| Group A | 20 | 11 | 9 |
| Group B | 21 | 7 | 14 |
| Group C | 31 | 13 | 18 |
| TOTAL | 71 | 31 | 41 |

P = 0,37

### 3.2.5 Apgar Scores

The Apgar scores recorded for babies in each group are shown in Table 3.9. Individual values are not shown but instead the scores are shown as the numbers of babies with values 6 or 5 points.

Statistical analysis (Fisher's Exact Test) did not show any differences between the groups. The one baby with a 5 minute Apgar score 5 subsequently died at 4 months of age of diarrhoeal disease. No further details are known of this child's development subsequent to his being discharged from hospital.

None of the babies had any clinical evidence of perinatal hypoxia before, during or after birth.

### 3.2.6 Radiological Findings

Only the babies who were hyperviscous (Group A and B) had a chest radiograph as it was considered unnecessary to expose the normal Group C infants to this procedure. The chest radiographs in Group A were also used to observe the position of the catheter tip used for the PPET. The majority were located in the inferior vena cava or at the entrance to the right atrium.

Babies in each group with abnormal chest radiograph findings are shown in Table 3.10. There are no significant differences (Fisher's Exact Test) between them ($p = 0,06$). The most frequent finding was increased vascularity (6 in Group A, 11 in

TABLE 3.9

APGAR SCORES AT 1 AND 5 MINUTES FOR THE GROUPS

| | n | 1 MINUTE | | 5 MINUTES | |
|---|---|---|---|---|---|
| | | ⩾ 6 | ⩽ 5 | ⩾ 6 | ⩽ 5 |
| Group A | 18 | 17 | 1 | 18 | 0 |
| Group B | 20 | 15 | 5 | 19 | 1 |
| Group C | 31 | 31 | 0 | 31 | 0 |

TABLE 3.10

RADIOLOGICAL FINDINGS

| | n | PLETHORA | ALVEOLAR INFILTRATES |
|---|---|---|---|
| Group A | 20 | 6 | 5 |
| Group B | 20 | 11 | 1 |

p = 0,06

Group B) and alveolar infiltrates (5 in Group A, 1 in Group B). The cardiothymic, thoracic ratio was $< 0,6$ in all cases. There was no association between clinical signs and radiological findings.

### 3.2.7 Electrocardiogram (ECG)

The numbers of babies in Groups A and B with an abnormal ECG are shown in Table 3.11. There was no significant difference ($p = 0,25$) between the groups. Amongst the 6 babies with abnormal ECG's, 4 had right atrial and 2 left atrial hypertrophy (Nadas and Fyler 1972). One baby had ST wave depression. The majority of babies had a normal ECG and there was no consistent pattern amongst those with an abnormal result.

### 3.2.8 Plasma Calcium Concentration

The mean $\pm$SD plasma calcium values (mmol/l) for the groups are shown in Table 3.12. All infants, with the exception of one baby in Group A, had values within the normal range (1,75 - 3 mmol/l (Teitz 1983). This infant had a plasma calcium value of 1,6 mmol/l. None of the babies with low or low normal levels had any clinical signs of hypocalcaemia.

The differences (analysis of variance) between plasma calcium levels in the groups is shown in Table 3.13. Hyperviscous babies had significantly lower (but normal) levels than those of the control infants.

TABLE 3.11

ELECTROCARDIOGRAM

| | n | ABNORMAL |
|---|---|---|
| Group A | 17 | 4 |
| Group B | 20 | 2 |

p = 0,25

TABLE 3.12

PLASMA CALCIUM VALUES (mmol/l) FOR THE GROUPS

| | n | MEAN | S.D. |
|---|---|---|---|
| Group A | 18 | 2,14 | 0,25 |
| Group B | 20 | 2,29 | 0,23 |
| Group C | 22 | 2,53 | 0,23 |

TABLE 3.13

PLASMA CALCIUM: COMPARISON BETWEEN THE GROUPS
(Analysis of Variance)

| | p VALUE |
|---|---|
| Group A / Group B | 0,055 |
| Group A / Group C | < 0,001 |
| Group B / Group C | < 0,001 |

### 3.2.9 Plasma Magnesium Concentration

Results of the mean $\pm$SD plasma magnesium values are shown in Table 3.14. None of the infants had levels below the normal range of 0,5-0,9 mmol/l (Teitz 1983).

There were no significant differences (Analysis of variance) in plasma magnesium values between the groups (Table 3.15).

### 3.2.10 Blood Glucose

None of the infants had hypoglycaemia when screened by Dextrostix (Aims) during the first 48 hours of life.

TABLE 3.14

PLASMA MAGNESIUM (mmol/l) FOR THE GROUPS

| | n | MEAN | S.D. |
|---|---|---|---|
| Group A | 16 | 0,74 | 0,14 |
| Group B | 20 | 0,77 | 0,17 |
| Group C | 22 | 0,85 | 0,31 |

TABLE 3.15

PLASMA MAGNESIUM: COMPARISON BETWEEN THE GROUPS (ANOVA)

| | p VALUE |
|---|---|
| Group A / Group B | 0,5 |
| Group A / Group C | 0,2 |
| Group B / Group C | 0,36 |

Comment on Study Sample

At this point in the study 3 groups of babies had been identified. These were a hyperviscous sample, half of whom (Group A) were allocated by random selection, to be treated with PPET while the other half (Group B) were not treated with PPET. The third group C were the non-hyperviscous control cases.

All three of these groups of babies had no significant differences between them with regard to anthropometric measurements, sex of infant, Apgar score, radiological, electrocardiac and plasma magnesium results.

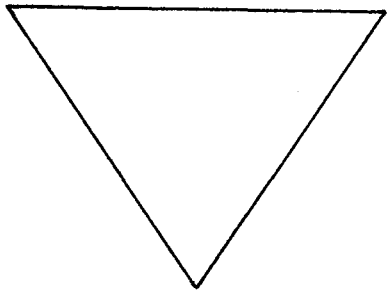
The major differences between them was the level of Hct and blood viscosity. Accordingly, the following triad could be constructed for the purpose of inter-group comparisons.

GROUP A

HYPERVISCOUS

AFTER PPET

n = 20



GROUP B

HYPERVISCOUS

n = 21

GROUP C

CONTROL

n = 31

3.2.11 Clinical Signs

Many of the babies had clinical signs which could have been attributed to the polycythaemia and hyperviscosity. The number of babies in each group are shown in Table 3.16. When the numbers of babies with clinical signs in each group were compared (Chi squared) (Table 3.17), there were no significant differences between Group A before PPET and Group B babies ($p = 0,15$). Treatment in Group A with PPET did not reduce the frequency of clinical signs ($p = 0,2$). Both hyperviscous Groups A (before and after PPET) and Group B, had significantly more symptomatic babies than the control Group C ($p = 0,001$, $p = 0,01$ and $p = 0,014$ respectively).

Details of the type of clinical signs seen in the groups are shown in Table 3.18. Amongst the newborns with MINOR signs 5 Group A infants had peripheral cyanosis which resolved following treatment with PPET. Signs of gastro-intestinal origin (e.g. poor feeding, vomiting and NEC) were most frequent in Group A pre and post-PPET and in Group B infants. This was particularly so in post-exchanged babies. Three of these babies had signs of early NEC which included abdominal distension, diminution of bowel sounds and the presence of fresh blood in the stool. They were treated symptomatically by stopping oral intake, preventing abdominal distension and were given antibiotics. A fourth baby developed frank NEC within 12 hours of the exchange transfusion. The baby progressed from signs of abdominal distension and ileus to pneumatosis intestinalis and perforation of the large bowel. An ileostomy was performed and this together with adequate supportive care and antibiotics resulted in a complete recovery. It was not

TABLE 3.16

CLINICAL SIGNS: NUMBER OF BABIES IN EACH GROUP

| | n | WITH | WITHOUT |
|---|---|---|---|
| Group A before PPET | 20 | 14 | 6 |
| Group A after PPET | 20 | 9 | 11 |
| Group B | 21 | 9 | 12 |
| Group C | 31 | 3 | 28 |

TABLE 3.17

CLINICAL SIGNS: COMPARISONS BETWEEN THE GROUPS

| | p VALUE |
|---|---|
| Group A / Group B before PPET | 0,15 |
| Group A before PPET / Group A After PPET | 0,2 |
| Group A before PPET / Group C | < 0,001 |
| Group A after PPET / Group C | 0,01 |
| Group B / Group C | 0,014 |

TABLE 3.18

CLINICAL SIGNS: FREQUENCY OF THE TYPE OF CLINICAL SIGNS IN THE GROUPS

| SIGNS | GROUP A BEFORE PPET | GROUP A AFTER PPET | GROUP B | GROUP C |
|---|---|---|---|---|
| Minor | | | | |
| Peripheral Cyanosis | 5 | - | 2 | - |
| Tremulousness | 2 | 5 | 2 | 1 |
| Lethargy | 5 | 2 | 1 | - |
| Hypotonia | 1 | - | - | - |
| Irritability | - | - | - | - |
| Poor Feeding | 2 | 1 | 4 | - |
| Vomiting | 4 | 7 | 5 | - |
| Major | | | | |
| Central Cyanosis | - | - | - | - |
| Respiratory Distress | 1 | 1 | - | 2 |
| Apnoea | - | 1 | 1 | - |
| Convulsions | - | - | - | - |
| GIT Signs | - | 4 | - | - |

clear whether the hyperviscosity or the exchange transfusion or both had resulted in the development of NEC in these babies.

Signs of central nervous system origin (tremulousness, lethargy, hypotonia and irritability) were less frequent. All Group C infants (except for one tremulous baby) were asymptomatic.

Several of the babies had signs classified as MAJOR. They were included in the study because these signs resolved rapidly and were not thought to have compromised the baby in any major way.

Of these infants, 3 babies had respiratory distress syndrome. One Group A baby had mild hyaline membrane disease and was tachypnoeic before and after PPET. Two Group C infants had tachypnoea for a short period only. Two infants (one Group A after PPET and one Group B) had a short period of apnoea. Both had a good response to resuscitative measures and the apnoea did not recur.

Four babies (Group A) had signs attributable to the gastro-intestinal tract and all of the signs occurred after PPET. One of these infants developed necrotizing enterocolitis with perforation of the large bowel. A defunctioning colostomy was performed and later closed after good recovery. At no stage did this baby become hypoxic or show signs of cerebral compromise. A second infant developed intestinal ileus with associated vomiting. There were no other signs of necrotizing enterocolitis and the baby's condition improved spontaneously after 24 hours. The 2 other babies developed transient

diarrhoeal disease which resolved in both cases after 24 hours.

Therefore, those babies with clinical signs which should strictly be classified as MAJOR were actually of a mild or transient nature. The one exception was the baby who developed frank necrotizing enterocolitis. This may have resulted either from the hyperviscous state or as a complication of PPET. In any event the complication occurred after random allocation and treatment with PPET.

No babies had seizures and there were no neonatal deaths.

3.2.12 Neonatal Behavioural Assessment Scale (NBAS)

The mean $\pm$SD age at which the Group A babies were tested was 12,3 $\pm$ 13,5 days, Group B 6,9 $\pm$ 2,9 days and Group C 11 $\pm$ 6,7 days. There are no significant differences between these ages (t Test).

The results of individual NBAS scores were analysed by grouping the 26 items tested into 4 'Dimensions' (Table 3.19). These 'Dimensions' were Interactive Processes, Motor Processes, Control of State and Stability with Stress. Profiles for each Dimension were selected according to the criteria outlined by Als et al (1977) such that scores were recorded as excellent, average or poor. The numbers of babies with their profiles in each group are shown in Table 3.20, 3.21, 3.22 and 3.23. Comparisons (Chi squared) between the groups could only be done for Interactive Processes and Control of State (Table 3.24 and 3.25). There were too few babies in the poor category of Motor

TABLE 3.19

DIMENSIONS AND BEHAVIOURAL SCORES OF THE NBAS

| DIMENSION 1: Interactive processes | DIMENSION 2: Motor processes | DIMENSION 3: Control of State | DIMENSION 4: Stability of stress |
|---|---|---|---|
| Orientation inanimate visual | General tone | Response decrement to light | Tremulous |
| Orientation inanimate auditory | Motor maturity | Response decrement to rattle | Startle |
| Orientation animate visual | Pull-to-sit | Response decrement to bell | Lability of skin colour |
| Orientation animate auditory | Defensive movements | Response decrement to pinprick | |
| Orientation animate visual and auditory | Activity | Peak of excitement | |
| Alertness | Hand to mouth | Rapidity of build-up | |
| Cuddliness | | Irritability | |
| Consolability | | Lability of states | |
| | | Self-quieting activity | |

TABLE 3.20

NBAS INTERACTIVE PROCESSES: NUMBER OF BABIES IN EACH PROFILE

| | n | EXCELLENT | AVERAGE | POOR |
|---|---|---|---|---|
| Group A after PPET | 20 | 6 | 6 | 8 |
| Group B | 19 | 5 | 9 | 5 |
| Group C | 29 | 18 | 10 | 1 |

TABLE 3.21

NBAS MOTOR PROCESSES : NUMBER OF BABIES IN EACH PROFILE

| | n | EXCELLENT | AVERAGE | POOR |
|---|---|---|---|---|
| Group A after PPET | 20 | 8 | 11 | 1 |
| Group B | 19 | 10 | 9 | 0 |
| Group C | 29 | 20 | 9 | 0 |

TABLE 3.22

NBAS CONTROL OF STATE: NUMBER OF BABIES IN EACH PROFILE

| | n | EXCELLENT | AVERAGE | POOR |
|---|---|---|---|---|
| Group A after PPET | 20 | 7 | 9 | 4 |
| Group B | 19 | 8 | 11 | 0 |
| Group C | 29 | 16 | 12 | 1 |

TABLE 3.23

NBAS STABILITY WITH STRESS: NUMBER OF BABIES IN EACH PROFILE

| | n | EXCELLENT | AVERAGE | POOR |
|---|---|---|---|---|
| Group A after PPET | 20 | 19 | 0 | 1 |
| Group B | 19 | 19 | 0 | 0 |
| Group C | 29 | 29 | 0 | 0 |

TABLE 3.24

NBAS INTERACTIVE PROCESSES: COMPARISONS BETWEEN THE GROUPS

| | p VALUE |
|---|---|
| Group A after PPET / Group B | 0,51 |
| Group A / Group C | 0,004 |
| Group B / Group C | 0,015 |

TABLE 3.25

NBAS CONTROL OF STATE: COMPARISON BETWEEN THE GROUPS

| | p VALUE |
|---|---|
| Group A after PPET / Group B | 0,12 |
| Group A / Group C | 0,12 |
| Group B / Group C | 0,43 |

Processes and of Stability with Stress to calculate meaningful statistics.

There are, however, significant differences between the dimension of Interactive Processes of Group A after PPET and Group C ($p = 0,004$) and also of Group B and Group C ($p = 0,015$). There are no differences between the groups when Control of State is compared . Only 1 Group A baby had a poor score for Motor Processes and only 1 for Stability with Stress.

Thus the main findings of the NBAS are that more hyperviscous babies (both Groups A and B) had significantly poorer scores in the Dimension of Interactive Processes, than did the control group.

### 3.2.13 Neurological Examination (Prechtl)

Neurological examination of the babies was done at approximately the same time as the NBAS (mean 10 days). Each baby's examination results were calculated according to an Optimal Score rating described by Prechtl and Beintema (1975). The maximal Optimal Score was 81 points. Analyses of the scores attained by the babies in each group are shown in Table 3.26. There were no statistical differences between the scores when the three groups were compared (Table 3.27). A second analysis was done by clustering babies with similar scores (Table 3.28). Most of the scores in all three groups fell between 45 and 59 points. There were no differences (Chi squared test $p = 0,85$) between the cluster scores of the groups.

TABLE 3.26

NEUROLOGICAL EXAMINATION OF PRECHTL: SCORES FOR THE GROUPS

| | n | MEAN | SD |
|---|---|---|---|
| Group A | 19 | 52,9 | 7,98 |
| Group B | 18 | 50,6 | 5,6 |
| Group C | 28 | 53,4 | 5,06 |

TABLE 3.27

NEUROLOGICAL EXAMINATION: COMPARISONS BETWEEN THE GROUPS (ANOVA)

| | p VALUE |
|---|---|
| Group A / Group B | 0,31 |
| Group A / Group C | 0,81 |
| Group B / Group C | 0,09 |

TABLE 3.28

NEUROLOGICAL EXAMINATION: SCORE FREQUENCY DISTRIBUTION

(Chi squared)

| SCORE | GROUP A | GROUP B | GROUP C |
|---|---|---|---|
| 60 - 64 | 2 | 1 | 3 |
| 55 - 59 | 5 | 3 | 9 |
| 50 - 54 | 3 | 7 | 10 |
| 45 - 49 | 4 | 4 | 4 |
| 35 - 44 | 3 | 3 | 3 |

P = 0.85

## 3.3 FOLLOW-UP

### 3.3.1 Developmental and Neurological Assessment at 32 Weeks

The infants in the three groups were followed-up and again assessed at approximately 32 weeks of age. Eighty five percent of all the babies (95% of Group A and 81% of groups B and C) were located for testing. Table 3.29 shows the mean $\pm$SD of the scores attained by the groups. When comparisons were made between the groups no differences were seen (Table 3.30). Thus at 8 months of age no differences in developmental achievements were evident between the groups. Neurological examination was also done at this time. None of the children had any defect detected.

### 3.3.2 Development At 2 Years of Age (Denver Developmental Screening)

When the children were approximately 2 years of age a home visit was done in each case.

Eighty five percent of the original sample were again traced and tested (95% of Group A, 85% of Group B and 74% of Group C). The remaining 17% could not be located. The Denver Developmental Screening test was scored according to the recommendations of Frankenburg et al (1971). Test results were either 'normal', 'questionable' or 'abnormal'. The number of children within each of these categories is shown in Table 3.31. There were no statistical differences between the groups (Table 3.32).

TABLE 3.29

DEVELOPMENTAL ASSESSMENT FOR THE GROUPS AT 32 WEEKS OF AGE

| | n | MEAN | SD |
|---|---|---|---|
| Group A | 19 | 99,9 | 6,8 |
| Group B | 18 | 99,3 | 8,3 |
| Group C | 25 | 103,4 | 2,3 |

TABLE 3.30

DEVELOPMENTAL ASSESSMENT: COMPARISONS BETWEEN THE GROUPS AT 32 WEEKS OF AGE

| | p VALUE |
|---|---|
| Group A / Group B | 0,789 |
| Group A / Group C | 0,067 |
| Group B / Group C | 0,055 |

TABLE 3.31

DENVER DEVELOPMENTAL SCREENING TEST

Numbers in each Group

| | 'NORMAL' | 'QUESTIONABLE' | 'ABNORMAL' |
|---|---|---|---|
| Group A | 18 | 0 | 1 |
| Group B | 15 | 3 | 0 |
| Group C | 22 | 1 | 0 |

TABLE 3.32

DENVER DEVELOPMENTAL SCREENING TEST:
COMPARISONS BETWEEN THE GROUPS

| | p VALUE |
|---|---|
| Group A / Group B | 0,557 |
| Group A / Group C | 0,555 |
| Group B / Group C | 0,43 |

### 3.3.3 Final Assessment at 6-7 Years of Age

The final follow-up assessment was planned to take place at the time when these children entered school for their formal education. Considerable difficulties were experienced in locating the sample children as many of the families had moved home. In all 87,5% (63/72) of the children were traced and tested. Of these 90% were from Group A, 85,7% from Group B and 87,1% from Group C.

#### 3.3.3.1 Anthropometric Measurements

Details of the mean age, weight, height and head circumference are shown in Table 3.33. The mean ages of the children were Group A, 7 years, Group B, 7,01 years and Group C, 7,24 years. When these ages were compared between the groups (Table 3.34) significant differences were found between Group A and C ($p = 0,01$) and Group B and C ($p = 0,03$). Thus the Group C children were significantly older than Groups A and B at the time of testing.

The weight, height and head circumference measurements were not statistically different amongst the groups except that children in Group C were taller than those in Group B. In addition Group A children had a smaller head circumference than did children in Group C.

TABLE 3.33

ANTHROPOMETRIC MEASUREMENTS (MEAN ± SD) AT FINAL TESTING

| GROUP | n | AGE (years) | WEIGHT (kg) | HEIGHT (cm) | HEAD CIRCUMFERENCE (cm) |
|---|---|---|---|---|---|
| A | 18 | 7 ± 0,30 | 21,11 ± 3,51 | 117,9 ± 6,87 | 50,65 ± 1,29 |
| B | 18 | 7,01 ± 0,47 | 20,93 ± 3,5 | 114,3 ± 6,55 | 50,86 ± 1,23 |
| C | 27 | 7,24 ± 0,22 | 22,37 ± 3,29 | 120,3 ± 5,22 | 55,52 ± 1,41 |

TABLE 3.34

ANTHROPOMETRIC MEASUREMENTS: COMPARISONS BETWEEN THE GROUPS
(p values)

| | AGE | WEIGHT | HEIGHT | HEAD CIRCUMFERENCE |
|---|---|---|---|---|
| Group A / Group B | 0,97 | 0,88 | 0,13 | 0,6 |
| Group A / Group C | 0,01 | 0,23 | 0,19 | 0,047 |
| Group B / Group C | 0,03 | 0,17 | 0,002 | 0,11 |

3.3.3.2 Percentiles

When each anthropometric measurement was plotted on growth percentiles 1 Group A, 2 Group B and 1 Group C children were found to be underweight. One each in Group A and B were overweight. Two Group A, 4 Group B and 2 Group C children were short of stature (NCHS, 1976). There were no children with micro or macrocephaly (Nellhaus 1968).

3.3.3.3 Parents' Educational Level

Table 3.35 gives the mean school standard attained by both the mother and the father of the children in the 3 groups. There were no statistical differences between the school standards attained by these parents.

3.3.3.4 Neurological Examination (Touwen)

The results of the neurological examination are the most important of the long term follow up data presented. It is here that neurological sequelae, which might have resulted from the polycythaemia and hyperviscosity at birth, would be expected to be found. The results also represent an end point to the study from which conclusions can be made. The results are shown in Table 3.36. The mean scores for the Groups A and B are 12,7 and 14,61 respectively and 8,7 for Group C. Comparisons between the groups are shown in Table 3.37.

Neurological comparison showed no differences between the hyperviscous Groups A and B. When Group A and Group B were compared with Group C, however, significant differences were found. Thus the hyperviscous groups whether treated or not at birth had a similar neurological examination at 6-7 years of age

TABLE 3.35

PARENTS' EDUCATION

Mean School Standard Achieved

| | MOTHER | FATHER |
|---|---|---|
| Group A | 4,9 | 5,1 |
| Group B | 5,1 | 5,4 |
| Group C | 6,0 | 6,6 |

p = 0,97

TABLE 3.36

NEUROLOGICAL EXAMINATION

| | n | MEAN | SD |
|---|---|---|---|
| Group A | 17 | 12,7 | 5,99 |
| Group B | 18 | 14,61 | 7,12 |
| Group C | 27 | 8,70 | 4,17 |

TABLE 3.37

NEUROLOGICAL EXAMINATION: COMPARISONS BETWEEN THE GROUPS

(Chi squared)

| | p VALUE |
|---|---|
| Group A / Group B | 0,38 |
| Group A / Group C | 0,016 |
| Group B / Group C | 0,003 |

and they scored significantly less well when compared with the control group.

None of the children had any gross neurological signs. In particular, there were no cases of epilepsy, paresis or spasticity. The most frequent abnormal findings were mirror movements in opposite limbs during unilateral neurological testing. This and a high incidence of dysdiadokokinesis in all 3 groups merely reflects the relative immaturity of motor control in these 7 year old children.

Specific neurological differences between the hyperviscous and control groups were sought. In no case could any one particular neurological deficit be elicited. There was thus a global difference between the groups, the hyperviscous children scoring less well than the controls.

In summary, children who had been hyperviscous at birth, whether treated or not had significantly poorer neurological scores than did children who had normal blood viscosity at birth. None of the children had any gross abnormal neurological finding.

3.3.3.5 Intelligence Testing using the New South African Individual Scales (NSAIS)

Results of testing with the NSAIS were expressed as Verbal, Non-Verbal and Full Intelligence Quotient Subtests. Table 3.38 lists mean $\pm$ SD for each of the subtest results in the groups. When these data are compared between groups (Table 3.39) no statistical differences are observed except that Group B children had lower non-verbal scores than Group C ($p = 0,03$).

TABLE 3.38

INTELLIGENCE TESTING: MEAN ± SD FOR EACH GROUP

| | n | VERBAL IQ | NON-VERBAL IQ | FULL IQ |
|---|---|---|---|---|
| Group A | 17 | 92,2 ± 14,7 | 98 ± 19,8 | 94,11 ± 17,6 |
| Group B | 18 | 92,3 ± 11,8 | 96,2 ± 13,2 | 93,6 ± 12,6 |
| Group C | 27 | 95,3 ± 11,2 | 105,5 ± 14 | 99,7 ± 13,3 |

TABLE 3.39

INTELLIGENCE TESTING: DIFFERENCES BETWEEN THE GROUPS (p VALUES)

| | VERBAL IQ | NON-VERBAL IQ | FULL IQ |
|---|---|---|---|
| Group A / Group B | 0,97 | 0,75 | 0,91 |
| Group A / Group C | 0,424 | 0,149 | 0,234 |
| Group B / Group C | 0,393 | 0,031 | 0,125 |

Further analysis was undertaken in an attempt to find differences between the groups. Individual scores were examined to detect Verbal/Non-Verbal intelligence quotient differences of greater than 15 points. Table 3.40 shows the number of children in each group with such differences. There were no statistical differences (Fisher's Exact test) when comparisons were made between the groups.

Finally, the mean values of each subtest of the NSAIS in Group C were used as a representative 'norm' for the other groups. Children in Groups A and B with scores less than the control Group C mean value minus 1 SD were counted and compared (Table 3.41). Again no statistical differences ($p = 0,67$) could be detected (Chi squared) between Groups A and B. Of the children who had scores less than 1 SD of the mean control value, only one child in Group A was mentally retarded. Her non-verbal IQ was 60, verbal IQ 47 and Full IQ 47.

In summary, there were no differences in NSAIS scores between the children who had been hyperviscous at birth, whether treated or not and the control children. The exception was that those children who had not been treated had a lower non-verbal IQ when compared with the controls. Only one child (Group A) had scores which were low and could be regarded as being subnormal.

3.3.3.6 Developmental Test of Visual Perception (Frostig)

The results of the tests for visual perception are shown in Table 3.42. The differences observed between the groups are shown in Table 3.43. When the results of Group A and B are

TABLE 3.40

INTELLIGENCE TESTING: VERBAL/NON-VERBAL DIFFERENCES > 15 POINTS

| | n | VERBAL > NON-VERBAL | VERBAL < NON-VERBAL |
|---|---|---|---|
| Group A | 4 | 3 | 1 |
| Group B | 3 | 2 | 1 |
| Group C | 6 | 6 | 0 |

p = 0,71

TABLE 3.41

INTELLIGENCE TESTING: NUMBER OF GROUP A AND B CHILDREN WHO SCORED < MEAN MINUS SD OF GROUP C CHILDREN

| | GROUP A | GROUP B |
|---|---|---|
| Verbal IQ | 7 | 6 |
| Non-Verbal IQ | 3 | 5 |
| Full IQ | 3 | 5 |

p = 0,67

TABLE 3.42

DEVELOPMENTAL TEST OF VISUAL PERCEPTION (MEAN ± SD) FOR CHILDREN IN THE GROUPS

| | n | MEAN ± SD |
|---|---|---|
| Group A | 17 | 98,9 ± 16,96 |
| Group B | 18 | 97,9 ± 15,8 |
| Group C | 27 | 108,7 ± 14,2 |

TABLE 3.43

DEVELOPMENTAL TEST OF VISUAL PERCEPTION: COMPARISONS BETWEEN THE GROUPS (t TEST)

| | p VALUE |
|---|---|
| Group A / Group B | 0,85 |
| Group A / Group C | 0,045 |
| Group B / Group C | 0,022 |

compared no differences are found. However, when the groups A and B are compared with Group C significant differences are found ($p = 0,045$ and $p = 0,02$ respectively).

In summary, both groups of children who had been hyperviscous at birth, whether treated or not, had significantly lower visual perceptual scores than the children who had not been hyperviscous at birth.

3.3.3.7 Fetal Growth Retardation and Outcome

A number of babies in Group A and B had been identified as being small for gestational age (SGA). These babies were unevenly distributed through the groups there being 2 in Group A and 9 in Group B. In order to test if these cases had lower outcome scores at 6-7 years of age their data was compared with that of those children who had grown appropriately at birth (AGA) (Table 3.44). No statistical differences (Fisher's Exact test) could be found between the groups. Thus growth retardation at birth did not appear to affect outcome at 6-7 years.

3.3.3.8 Regression Analysis of Neonatal and Follow-up Data

Regression analysis was done on the data to derive the form $y = Ax + B$. The significance of r was derived from appropriate tables.

This analysis was done on data which would be used to test the Null Hypothesis: The Hct and blood viscosity at birth do not correlate with outcome (behavioural, neurological, developmental, intellectual or perceptual) in later life.

TABLE 3.44

NUMBER OF CHILDREN WITH SUBOPTIMAL NEUROLOGICAL, INTELLECTUAL AND PERCEPTUAL SCORES WHO WERE SGA AT BIRTH

| | | n | TOUWEN | NON-VERBAL IQ | VERBAL IQ | FULL IQ | FROSTIG |
|---|---|---|---|---|---|---|---|
| Group A | AGA | 18 | 2 | 4 | 1 | 1 | 1 |
| Group A | SGA | 2 | 0 | 1 | 2 | 2 | 2 |
| Group B | AGA | 12 | 1 | 2 | 3 | 2 | 1 |
| Group B | SGA | 9 | 1 | 4 | 2 | 2 | 5 |

AGA = Appropriate for gestational age

SGA = Small for gestational age

The only significant correlation was in the Control Group C between Hct and non-verbal IQ at 6-7 years of age ($p = < 0,05$). No other associations were found so that the Null Hypothesis is accepted, namely that there is no correlation between central venous Hct or whole blood viscosity and outcome in later life.

# PART IV

# DISCUSSION

## CHAPTER 1 : METHOD OF SAMPLING

The results of this part of the study confirm the findings of Linderkamp et al (1977) and Oh and Lind (1966) showing the necessity for warming the heel before Hct sampling in the newborn. Haematocrit determinations from an unwarmed heel are largely unreliable and overestimate the true central venous value by 11,5%. Alternatively, warming the heel improves the capillary-venous relationship so that the mean difference between them is only 2%. This is also shown by an improved correlation coefficient (r) of 0,78 to 0,95. Thus, where central venous blood samples are difficult to obtain, a warmed heelprick Hct will give a good approximation of the central value. Care must still, however, be exercised as the warmed heel prick Hct may be as much as 8% higher than the central value or may be 4% less than this value.

An interesting observation is that although the biological differences between the warmed heelprick and central venous Hct are small (2%), statistically they are different ($p < 0,001$). This is due to the large range in the values obtained.

Very few laboratories attached to newborn nurseries are equipped to measure blood viscosity. The relationship between the Hct and the viscosity are therefore important. The intention of the analysis

performed to construct Table 1.3 was to present data which may be used to predict the likelihood of high blood viscosity from the Hct.

When the Hct was obtained from an unwarmed heel and found to be 65% then all of the babies who were hyperviscous were identified (sensitivity). However, neonates with a normal blood viscosity were also included in this group and thus falsely identified. A positive predictability value of 26,2% confirms this high false positive prediction. Warming the heel of the baby greatly improved the positive predictability so that 68% of the hyperviscous babies were identified. When blood from a central vein was used there was a 91% positive prediction that the baby would be hyperviscous. Clearly the Hct from blood obtained by venisection of a central vein gives the most useful information but warming the heel before sampling also provides a good indication of the level of the viscosity. Not all neonates with a central venous Hct $\geqslant$ 65% are necessarily hyperviscous (positive prediction 91%) and, alternatively, not all hyperviscous babies are polycythaemic (sensitivity 91%). Nevertheless, the Hct, if properly performed, is a useful guide to the presence of high blood viscosity in the newborn.

# CHAPTER 2 : NORMAL VISCOSITY VALUES

A review of the literature for normal viscosity data in the newborn was undertaken so as to be able to identify hyperviscous babies and also to see if data for the local population were similar to those of other studies.

Of the 5 papers reviewed, there was very little consensus amongst the authors as regards normal values. There was also little uniformity with regard to the site of blood sampling (umbilical cord, cubital vein, dorsal hand vein blood etc), the age of the patient, or the relationship of the viscosity to haematocrit values $\geqslant$ 65%. What is needed is a well controlled and detailed study of normal babies.

Shohat et al (1984(a)) have begun to address this problem by documenting normal viscosity and Hct values. Their study examined babies in the first 18 hours of life and showed considerable variations during this time. Data are needed for the first 4-5 days at least and possibly longer. The results of the 10 babies studied in this thesis clearly show variations with time and sample site. These data cannot be considered representative of the population because of the small sample. A larger and longer study is needed.

The International Committee for Standardisation in Haematology has prepared guidelines on the measurement of blood viscosity and erythrocyte deformability (Stuart, 1987). It is hoped that bodies of this nature will be instrumental in improving the quality of normal blood viscosity and other rheological data.

# CHAPTER 3 : HYPERVISCOUS TREATMENT STUDY

## 3.1 INTRODUCTION

The aim of this study was to determine whether treatment with PPET was of benefit to NPHV newborns who had minor or no clinical signs during the neonatal period. This was to be measured longitudinally from birth to 6-7 years of age. The findings of an increased incidence of serious GIT signs following PPET and the lack of clinical improvement at this time argue against the use of PPET. When these hyperviscous babies were followed-up until the age of 6-7 years and tested, comparison with a control group showed that they performed less well in neurological, non-verbal IQ and visual perception. The group of hyperviscous babies treated by PPET at birth were no better than those not exchanged. This suggests that the cause of the hyperviscosity rather than the effect may be responsible for the adverse clinical signs and poor outcome in later life.

## 3.2 SAMPLE SELECTION

Babies selected for the Hyperviscosity Treatment Study were initially identified because they appeared clinically plethoric. Therefore, not all babies born during the period of study were necessarily tested for NP or HV. For this reason it was not possible to calculate the incidence of NPHV for the community. The method of selection of subjects also makes it difficult to compare the results of this study with the findings of others. Black et al (1985(a)) took all infants born in their hospital over a 2 year period as being eligible for study. This

method of patient selection would result in a different sample and the findings of the 2 studies would not therefore be truly comparable. The causes of NPHV may not have been the same in both studies and this could lead to different results, and different conclusions. It has not been possible in this or in any other published studies to determine the precise cause of NPHV. It seems logical that the reason for, or the cause of, the hyperviscosity would have an effect on the neurodevelopmental status in later life. Babies who have NPHV due to a blood transfusion (passive) would probably be less mentally affected than those who have suffered chronic intrauterine hypoxia (active). This hypothesis was considered at the outset of this study and an attempt was made to separate the causes of NPHV by the measurement of plasma erythropoietin. A brief description of the method used and the results obtained are included in the Appendix. It was felt at the time that the method was imprecise and that there was no reference data against which the values of the study babies could be compared. The test was therefore considered unreliable and was not used in the thesis data. It was thus not possible to determine the causes of NPHV in babies studied. This is a major deficiency in this and all other studies on the outcome of NPHV to date and is an aspect that needs to be studied further.

The inclusion in this study of a control group (Group C) was considered important. The control group was representative of the general population from which the study Groups A and B had come and so provided a standard of comparison. In many aspects no comparative data was available for the population sample under study and particularly not for blood viscosity, neonatal

behaviour and developmental achievement. It was also considered necessary to have a matched control group who would grow up in parallel with the NPHV infants and be subject to the same socio-economic influences. The Control Group is therefore a comparative group but does not necessarily represent a 'normal' group. However, in most respects the control group was normal!

The size of the sample studied for each of the study groups was small. This may have affected results and conclusions of the study. The original randomisation allowed for more patients, but the numbers had to be reduced for various reasons: the time available and the opportunity for case collection limited the numbers. One infant with severe hyaline membrane disease was considered too ill for randomisation of treatment; another had Down's Syndrome; several were excluded because they were Black and not of mixed race. Social and political circumstances made it impossible to follow these children adequately and many (6 out of 7) were lost to follow-up. It was felt at the time, that the babies born into families of mixed race would be easier to follow and would form a more homogenous sample. Although there were considerable difficulties in tracing the children for follow-up 87% of the original sample were finally tested at 6-7 years of age. Black et al (1985(a)) estimated from their earlier data that 70 sample patients would be necessary to determine significant differences between treatment groups. Other studies on the treatment of NPHV have used small numbers. Wood (1959) quoted 2 cases, Gatti et al (1966) 10, Kontras (1972) 8, Mackintosh and Walker (1973) and Gross et al (1973) 30. More recently the Denver group (Black et al 1982(c), Goldberg et al 1982 and Black et al 1985(a)) have published

larger series but as stated earlier, these studies are not strictly comparable because of the method of patient selection.

In summary, although the numbers of study cases in this thesis are small, the high percentage follow-up recall, the strict objectivity of measurements and the thoroughness of testing allow for a reasonable degree of confidence in the results.

## 3.3 ANTHROPOMETRIC DATA

Comparisons between the measurements of gestational age, weight, length and head circumference amongst the groups at birth were remarkably similar. Although no statistical differences could be shown between the groups, when the individual babies' weights were plotted on percentile graphs (NCHS, 1976) 27% of the NPHV babies were small for gestational age. These babies were unevenly distributed between the groups, there being more in Group B than in Group A.

Several authors have noted the association of fetal growth retardation and NPHV. Gross et al (1973) observed the association but did not comment on its effect on outcome. Høst and Ulrich (1982) found a significant number of SGA babies as did Black et al (1982(a)) in their study. Again no attempt was made to examine the outcome in these cases.

Hakanson et al (1983) clearly showed an association between SGA infants, NPHV and the presence of NEC. Humbert et al (1969) also observed the association between SGA babies, polycythaemia and clinical signs. Clearly these infants are more at risk than

appropriately grown babies and warrant special attention at the time of birth.

## 3.4 THE SEX OF THE INFANT

As in other studies (Black et al 1982(a)), no correlation could be shown between the sex of the infant and the presence of hyperviscosity.

## 3.5 APGAR SCORE

It is important in a study of this nature to eliminate, as far as possible, variables which are likely to have a direct or obvious effect on the later neurological outcome of the children. Amongst these, perinatal hypoxia should be excluded. The Apgar Score results, although a poor marker of asphyxia neonatorum (Sykes et al 1982), did not indicate that any of the babies (except one who later died at 4 months) were affected. In addition, the lack of signs of post-asphyxial encephalopathy (Levene et al 1986) would make it highly unlikely that any baby suffered perinatal hypoxia at birth.

## 3.6 RADIOLOGICAL FINDINGS

Radiological abnormalities were frequent in both Groups A and B but associated clinical signs were absent. Wesenberg et al (1977) also noted frequent findings of increased vascularity, alveolar infiltrates and also hyperaeration amongst hyperviscous neonates. They commented that these findings would probably have been missed because of the lack of clinical signs in these babies. Gatti et al (1966) also reported radiological findings. Cardiomegaly and increased vascular markings were the main features observed in their series of NPHV babies.

## 3.7 ELECTROCARDIOGRAM

The electrocardiogram has not proved helpful in NPHV (Goldberg et al 1982). No consistent changes have been reported. Findings of this study concur with these observations. Echocardiography, however, may be a more useful investigation. Geierman et al (1979) have shown significant changes in the right ventricular pre-ejection period to right ventricular ejection time ratio. Such changes occurred until 72 hours of age in affected infants and were 30% less following PPET.

## 3.8 PLASMA CALCIUM AND MAGNESIUM

The main object of the plasma calcium and magnesium determination was to be able to comment on these values should the NPHV infants have experienced convulsions or tremulousness in the immediate neonatal period. Several babies had low normal plasma calcium and magnesium values but were not associated with clinical signs. Goldberg et al (1982) reported normal plasma calcium in NPHV neonates while Gross et al (1973) had one case of hypocalcaemia in a series of 18 babies. It is not known why the plasma calcium and magnesium values were low-normal in this study or if NPHV had a direct effect on these values.

## 3.9 CLINICAL SIGNS

Selection of study cases with NPHV depended to a large degree on the severity of clinical signs. These were divided into those considered to be less serious (MINOR SIGNS) and those thought to be more serious (MAJOR SIGNS). This was done on the basis of assigning complications which would be more likely to have a serious long-term effect (e.g. central cyanosis, respiratory

distress, apnoea, etc) on the infant to the MAJOR category. Accordingly babies with NPHV and less serious complications (e.g. peripheral cyanosis, tremulousness, lethargy, etc) were assigned to the MINOR category.

Many of the babies in groups A and B had clinical signs attributable to NPHV. Hyperviscous babies, whether exchanged or not, were significantly more symptomatic than were the control babies. It was hoped that there would be fewer signs after PPET but this was not found to be the case. Tremulousness and vomiting were more frequent in these infants. Peripheral cyanosis, however, did disappear after exchange. The increased incidence of gastrointestinal signs following PPET was a matter of concern and in particular the occurrence of frank NEC in one baby. This baby had a Hct of 65% and was mildly hyperviscous. The tip of the umbilical vein catheter was confirmed radiologically to be in the inferior vena cava before the exchange procedure was commenced (Baker et al 1969). Whether the polycythaemia per se or the exchange procedure itself caused the NEC is not clear. A recent report (Thangavel et al 1982) describes a case of an infant who developed NEC following exchange transfusion where the catheter tip was located in the inferior vena cava. Alternatively, Hakanson and Oh (1977) reported on the association between NEC and hyperviscosity and postulated the mechanism to be bowel ischaemia. Black et al (1985(b)) found a significantly greater incidence amongst patients treated with exchange transfusions when compared with patients who were treated symptomatically or in control subjects (i.e. no PPET). They state that in the absence of clear

evidence that PPET improves outcome in NPHV its use must be carefully evaluated in each case.

A further consideration with regard to clinical signs and to the risk of NEC, is the technique used for the PPET. The usual procedure has been to insert a catheter through the umbilical vein into the inferior vena cava via the ductus venosus. The withdrawal of blood and the infusion of plasma are both done via this route. Placement of the catheter tip can be extremely important (Baker et al 1969) since exchange solutions (in this case fresh plasma) may find their way to the liver, spleen or GIT. This, in turn, may cause damage or compromise the function of that organ (Touloukain et al, 1973). This may result in NEC should the GIT be involved. It would, therefore, seem wise to adapt the technique of exchange transfusion so that fluids are not infused via the umbilical route. Instead, the plasma could be given rapidly through a peripheral vein (e.g. scalp vein) while an equal volume of blood is drawn from the umbilical vein catheter (tip site now less important). The procedure can usually be done in 5-10 ml of blood aliquots and takes approximately 30 minutes to complete. This method avoids the administration of fluids into the umbilical vein or beyond and in clinical practice has not been associated with GIT signs. Recently Charlton and Phibbs (1983) published experience of peripheral vein partial exchange transfusion in 12 polycythaemic infants. Their results were encouraging but there were problems in the withdrawal of venous blood from peripheral sites. Nevertheless, this form of exchange transfusion warrants further assessment.

In the absence of clear evidence that treatment with PPET significantly improves the outcome in these relatively asymptomatic hyperviscous infants, the risk of gastrointestinal complications should be carefully evaluated. Unnecessary exchange transfusions and subsequent complications may be avoided if this policy is adopted.

The incidence of signs in the babies of this study differed from that of other reports but the variety of signs was similar to that in previous reports. Gross et al (1973) observed a high incidence of cyanosis and jitteriness. In addition, five of 18 affected babies had seizures. Black et al (1982(a)) reported tachypnoea, cyanosis, NEC and hypoglycaemia more frequently. Høst and Ulrich (1982) in their series of 635 infants with NP had only 13 mildly symptomatic infants, all of whom subsequently did well. Recently, Black et al (1985(a)) showed hypoglycaemia, cyanosis and apnoea to be more common in hyperviscous infants. Several babies in their series had severe clinical signs. These included apnoea, seizures and signs of hypoglycaemia. In all these quoted studies patient selection was different to that of this study and this makes comparisons difficult.

In summary, in this study the hyperviscous babies were more symptomatic than controls. Neonates undergoing PPET had more gastrointestinal problems including NEC than did those not exchanged. Clinical signs seen in the babies of this study were as a rule milder than those reported in other studies.

## 3.10 NEONATAL BEHAVIOURAL ASSESSMENT SCALE (NBAS)

The NBAS has become internationally accepted as a measure of behaviour in the newborn period. Brazelton (1973) proposed that the test in the neonate 'may reveal some of the precursors for his later personality development'. The test was applied in this study in order to gain a measure of the effects of NPHV on neonatal behaviour.

Ideally, the test should have been done repeatedly on the same infant during the period the baby was hyperviscous, or before and after treatment. This would have given a better measure of behavioural dysfunction and recovery. The test, as done in this study at 10 days of age, constitutes a measure of the behavioural state when the baby has had time to settle or to recover from the effects of PPET (Group A), and to adapt to the hyperviscous state (Group B).

The observation of differences in Interactive Processes amongst the NPHV babies when compared with the control Group C is important. Interactive Processes measure the baby's ability to communicate with the outside world and particularly with those who care for him. This dimension includes the measurement of the ability to respond to sound, sight and to being handled. Since many mechanisms of maternal-infant bonding (Klaus and Kennel 1976) depend on these responses, disturbance of these behavioural abilities in the neonate with NPHV, could be a disadvantage. These mother-infant pairs may not benefit from adequate bonding after birth which could lead to problems in later life. This is an aspect which deserves further study,

especially in view of recent challenges of the importance of bonding by Lamb (1982).

Only one paper (Goldberg et al 1982) has examined the behavioural performance of NPHV Infants using NBAS. Examination of the babies at 8 hours of age clearly differentiated hyperviscous babies from controls. The test did not show significant differences between babies who were treated with PPET and those who were not. Repeated testing at 1,3 and 14 days did reveal differences. The most consistent findings were lethargy and hypotonia. Further analysis of the data showed that exchanged babies had improved motor maturity, less tremor and fewer startles, orientated better and were more alert and active. By 2-3 weeks of age the exchanged group had better motor maturity and orientation responses. The non-exchange group had sustained ankle-clonus and incomplete Moro reflexes.

It is therefore clear that NPHV affects behavioural patterns, particularly in the dimensions of interactive and motor behaviour. Treatment with PPET may be of benefit to affected babies.

The reason for this disturbance in behaviour is not apparent. Lethargy is a well recognised sign of NPHV and this would explain the findings of the NBAS testing. The reason for the lethargy may be a decrease in CBF with relatively poor oxygenation. The study by Rosenkrantz et al (1984) on CBF and oxygen content (see Review) argues against this explanation. Further studies are needed to answer this question.

## 3.11 NEUROLOGICAL EXAMINATION

The neurological examination (Prechtl and Beintema 1975) was done at about the same time as the NBAS. The objectives were to identify neurologically compromised babies amongst those with NPHV. The results did not show differences between the groups. Goldberg et al (1982) in her paper examined NPHV babies at 8,24 and 72 hours and again at 2 weeks of age. At 8 hours, test results amongst NPHV babies differed from controls. The NPHV babies in general had more problems with muscle tone and with feeding. These problems had disappeared by 24 hours of age. Early neurological examination therefore may be abnormal in affected babies.

## 3.12 FOLLOW-UP

In order to obtain a high percentage of follow-up amongst the study and control subjects, frequent contact was made with the families. This was done through regular mailing and home visits. Several families moved home without leaving forwarding addresses. Many of these families were located again through contact with their friends, schools, community health centres and housing officers. A few children, however, were inevitably lost to follow-up. Some were not found for the earlier developmental testing but were found for later pre-school assessments. In the main, most children were followed longitudinally from birth till 6-7 years of age.

## 3.13 DEVELOPMENTAL AND NEUROLOGICAL ASSESSMENT AT 36 WEEKS

Both the developmental and neurological evaluation scores of the children in Groups A and B at 36 weeks of age were within the

limits obtained for the control Group C. No gross neurological abnormalities were detected in any of the children. This is in direct contrast to the work of Goldberg et al (1982) who found a high percentage of neurological abnormalities, including spastic diplegia, in children who had had NPHV at birth.

They also identified 3 children amongst their hyperviscous group who had low Bayley Mental Developmental Scores at this time.

The results of the two studies differ considerably in their findings of developmental and neurological achievement at 36 weeks of age. This is mainly due to the method of case recruitment at birth, more severe subjects having been chosen for the Goldberg et al (1982) study.

3.14 DEVELOPMENT AT 2 YEARS OF AGE (DENVER DEVELOPMENTAL SCREENING)

When the children were 2 years of age a home visit was done by the author and the Denver Developmental Screening Test applied. Again no differences could be found between hyperviscous and control children. The home visit was done mainly to maintain contact with the children and their families. The Denver Developmental Screening Test was used because of its speed and ease of application. The results of the test confirmed the findings of earlier testing (36 weeks) where no delays were apparent in the Groups A and B.

3.15 ANTHROPOMETRIC MEASUREMENT AT 6-7 YEARS OF AGE

An important consideration in the results of testing at this time was the ages of the children in each of the groups.

Unfortunately Group C children were slightly older (approximately 3 months) than the other groups so possibly better able to perform the tests. This was particularly so with the Touwen neurological test which could not be controlled for age. The other tests (NSAIS and Frostig) were both controlled for age.

Generally the children in the 3 groups were very similar when the anthropometric measurements corrected for age were considered. The exceptions were that Group B children were shorter and Group A children had smaller heads than Group C. No children were dwarfed or had microcephally.

## 3.16 PARENTS' EDUCATIONAL LEVEL

When assessing development and intelligence amongst the children it was important to have a measure of the child's environment and in particular the educational standards of his or her parents. The children in all 3 groups came from parents with very similar educational attainments. Thus it is reasonable to assume that test differences would not be greatly affected by the different educational standards of the parents. Other variables not controlled for (e.g. income, social class) may have had an effect but this information was not available. Income, education and social class are in any event related (Reiss 1961, Brand 1976).

## 3.17 NEUROLOGICAL EXAMINATION (TOUWEN)

The results of the follow up examinations at 7 years of age and particularly of the neurological examination, are important in

that they represent the end point of the study and data against which conclusions and recommendations can be made. The documentation of significant neurological differences between the children who had been hyperviscous at birth and those who had not is a major finding in this study. Clearly, although not necessarily directly related, the hyperviscosity at birth probably contributed to the lower scores seen in these children. The treatment of neonatal polycythaemic hyperviscosity (NPHV) with PPET gave no associated benefits to the long-term outcome in these children. Although it was possible to show differences between the neurological scores of children who had NPHV at birth and those who did not, none of the affected children had any gross neurological defects. Although the number of babies initially studied was small, the fact that a high percentage were followed to 7 years of age serves to strengthen the value of the results. These findings differ from those of other studies. Black et al (1982(a)) followed 78 of 111 hyperviscous infants until they were 2 years of age. In this retrospective study, she found 25% of the hyperviscous children to have neurologic abnormalities when compared with 6% of the controls ($p < 0,005$). Spastic diplegia was common while hypotonia was also common. There were also cases of hemiparesis, athetosis and of seizures. Of note was the fact that the presence of neurologic signs did not appear to be affected by treatment with PPET. Motor delays were as frequent amongst children who were hyperviscous at birth and treated with PPET with those who were not treated.

At the same time Goldberg et al (1982) reported on 20 hyperviscous babies randomly assigned to treatment with PPET or to observation only. They were compared with 10 controls and followed to 8 months of age. Neurologic abnormalities at that time were impressive and included tremors, spastic diplegia and monoparesis in 9 of 16 cases followed. No distinction was shown between those treated and those observed.

The 2 studies mentioned above both document neurological abnormalities in children who had been hyperviscous at birth. It would appear that there is a cause and effect association between NPHV and neurological outcome. Alternatively, another factor may be responsible which caused the neurological damage and the NPHV. Reversing the NPHV may not necessarily improve the neurological outcome. In both studies, treatment with PPET was not shown to be of benefit or to improve the outcome in these children. Therefore, neither of the authors could recommend treatment with PPET for NPHV at birth.

In another study from Denmark, Høst and Ulrich (1982) followed up 117 polycythaemic (Hct range 60-72%) untreated babies examining them at 2 years and obtaining a questionnaire assessment at 6 years of age. Very few children had problems and those that did had problems that appeared unrelated to the haematocrit levels. Amongst the 117 babies studied, 30 had Hct values greater than 65%. Although viscosity studies were not done at birth and the 6 year assessment was done by questionnaire, it was concluded that haemodilution was not indicated in NP with minor or no symptoms. The methodology of

this study, however, leaves the results and conclusions open to question.

Of all the studies on NPHV reported in the medical literature that of Black et al (1985(a)) in Denver is the most pertinent for comparison with this study. In many respects the two studies are very similar except for the manner in which the patients were selected. This is the key difference between the two studies and probably accounts for the different findings. Comparison of the number and severity of neurological signs in the babies shows these to be considerably greater in the Denver study. Ninety-three of the Denver NPHV infants were randomly assigned either to treatment with PPET or to observation only, and the children evaluated at 2 years of age. The group receiving PPET had fewer neurological disorders and fewer fine motor abnormalities than did those who were not treated. The authors commented that the handicaps were mild and that they did not know whether these would interfere with cognitive function in later life.

Although the authors recommend treatment with PPET for NPHV, it must be clearly stated that this advice is concluded from a study in which the subjects had MAJOR signs at birth. Many of their babies had treatment associated gastrointestinal complications (Black et al 1985(b)) and for this reason may not necessarily have benefitted from PPET.

In conclusion, results of this 6-7 year follow-up study show that NPHV babies, whether treated with PPET or not, have lower

neurological scores when compared with a matched control group. Those hyperviscous babies with no apparent signs or only minor signs did not have any gross neurological deficiencies in later life.

3.18 INTELLIGENCE TESTING (NSAIS)

The results of the NSAIS testing showed that, in general, children who had NPHV at birth whether treated with PPET or not, performed as well as the non-hyperviscous control group. The exception was that non-treated hyperviscous Group B children had significantly lower non-verbal scores. These findings relate to problems with visual perception also noted in this group (see later Frostig). It must be pointed out that these Group B children still had non-verbal scores within the normal range, but had a lower mean score when compared with Group C.

In applying the test, efforts were made to minimise the influences of social factors, tester bias and tester rapport. Social factors such as class, income, housing etc (although not recorded) were assumed to be equal in the groups as the children had all grown up in parallel conditions in the same local community. Social factors were, therefore, likely to be similar. Educational attainments of the parents were also similar and unlikely to have an effect on the NSAIS results. Finally, the examiner administering the NSAIS was unaware of the patient group and always ensured that proper rapport was established in each case.

In summary, children (aged 6-7 years) who were hyperviscous at birth had intelligence scores comparable with a non-hyperviscous control group. Treatment with PPET did not improve the overall outcome but may have resulted in more optimal non-verbal scores in the treated group.

## 3.19 VISUAL PERCEPTION (FROSTIG)

Testing for visual perception again showed that the children who had been hyperviscous at birth whether treated with PPET or not, scored less well than the control group. There was no difference between the treated and non-treated groups.

Children with visual perceptual problems (Frostig et al 1964(a)) are likely to have associated learning problems as well as non-verbal intelligence score differences. This relationship was seen in the non-treated Group B children and warrants further study.

## 3.20 OUTCOME AND GROWTH RETARDATION

Several babies had suffered intrauterine growth retardation and were small for gestational age at birth. The possibility that this disturbance in growth in these babies might have had an effect on later outcome was explored. No such differences were found. Therefore, the differences noted between the groups A and B compared with Group C are not due to growth retardation. The inference is that these differences are more likely to be due to the hyperviscous state present at birth.

# PART V

# SUMMING UP

## CHAPTER 1 : SUMMARY OF FINDINGS

The following are a summary of the main findings of the study:

1. METHOD OF SAMPLING

In the newborn infant, a Hct determination made from an unwarmed heel prick sample gave a higher value (mean 11,5 - 18,3%) than that of a central venous sample.

When the heel was warmed, the capillary-venous relationship improved considerably so that the average difference was only 2%.

If the Hct value was $\geqslant$ 65%, whether the sample was taken from a warmed heel or a central vein, then it was likely that the baby would be hyperviscous.

2. NORMAL VISCOSITY VALUES

There is little consensus amongst authors of publications in the international literature as to what constitutes normal whole blood viscosity in the newborn infant.

Normal Hct and viscosity values of babies born in Cape Town most closely approximated those of Gross et al (1973) for umbilical cord blood, and Mackintosh and Walker (1973) for venous blood on the first day of life.

Normal blood viscosity of babies born in Cape Town was initially found to be low in umbilical cord blood, but rose after approximately 12 hours of age and remained constant over the next 4 days of life.

3. HYPERVISCOSITY TREATMENT STUDY

Amongst the newborns with NPHV, there was a high incidence of babies (26%) who were small for gestational age.

Radiological signs in the chest (increased vascularity and alveolar infiltrates) were present in 39% of NPHV infants. These signs did not correlate with the presence of clinical disease.

The plasma calcium and magnesium levels in the NPHV infants were low normal or low. The values in individual infants did not correlate with clinical signs.

Clinical signs were more frequent in NPHV infants. Most of these were of a MINOR nature. Amongst those considered to be MAJOR, gastrointestinal signs were most common, particularly those of necrotizing enterocolitis. These signs only occurred in those babies who had undergone PPET.

Behavioural assessment (NBAS) in the neonatal period revealed a number of babies who had interactive problems.

The follow-up at 36 weeks and 2 years of age of the children who had been NPHV at birth whether they had been treated with PPET

or not, did not show differences between them. Neither of the developmental assessments that were administered identified children who might have problems in later life.

The final assessment of the children when they were 6-7 years of age showed that those who had had NPHV at birth, were significantly different from normal control children who had not been affected. Specifically, there were significantly lower neurological, non-verbal intelligence and visual perceptual scores amongst those who had been hyperviscous at birth. Treatment of NPHV Infants at birth by PPET did not improve the outcome at 6-7 years of age when compared with non-treated but affected children.

## NULL HYPOTHESIS

The null hypothesis for this study, which stated that there would be no difference in the outcome of hyperviscous newborns with no apparent or only minor clinical signs, whether treated or not treated with partial plasma exchange transfusion, is accepted.

# CHAPTER 2 : CONCLUSIONS AND RECOMMENDATIONS

## 1. METHOD OF SAMPLING

The major problem with heel prick capillary Hct determinations in the newborn is that they give higher values than the central venous sample. Care must therefore be taken to warm the heel, preferably in warm water at 40°C for 5 minutes. A warmed heel sample can be used reliably to approximate a central venous value. However, the warmed heel value does not relate absolutely to the central venous value. It is also recommended that the warmed heel prick Hct and/or central venous Hct of $\geqslant$ 65% be used to predict the presence of hyperviscosity when viscometry is not available.

## 2. NORMAL VISCOSITY VALUES

Because of the lack of consensus in published data on what constitutes normal neonatal viscosity values, a detailed controlled study should be undertaken. The recommendations of the International Committee for the Standardisation of Haematology (Stuart, 1987) are a welcome start in this direction.

Normal whole blood viscosity data is required for both term and preterm infants from birth until at least 7 days of age. The data should be controlled for the site of blood sampling, the age of the baby (especially during the first 24 hours) and the method of Hct determination. Details of time of cord clamping, the altitude above sea level and the clinical well-being of the study babies are also important considerations.

## 3. HYPERVISCOSITY TREATMENT STUDY

It is clear from the results of the study that NPHV infants are at risk of sequelae and that treatment with PPET does not improve their outcome.

Polycythaemia and associated hyperviscosity are common complications in fetal growth retarded infants. For this reason, babies who are small for gestational age should have a haematocrit determination done soon after birth and should be observed carefully for the occurrence of polycythaemia in the first week of life. These infants are reportedly more likely to develop NEC (Hakanson and Oh, 1977).

The investigations done on NPHV infants in this study were not of particular value in the assessment of the babies. The chest radiograph, the electrocardiogram and the plasma calcium and magnesium were in general more frequently abnormal or there were low values in the study babies. These results did not help in the clinical diagnosis or in the management of the baby.

Clinical assessment in the neonatal period using the NBAS was useful in that it identified hyperviscous babies who might have problems with mother-infant bonding. Special efforts should be made to encourage contact between these babies and their mothers to promote bonding.

The 36 week and 2 year assessment was more useful as a family contact opportunity than it was as an appraisement of the

child's developmental status. It is not clear why these assessments did not identify problem children at this age, but the subtle nature of the defects found later may not have been apparent at this time. The tests used at different ages also measured different abilities in these children. Assessment at between 6-7 years of age showed that the children who had been hyperviscous at birth functioned neurologically, intellectually and perceptively less well than a matched control group. Treatment with PPET did not improve outcome. Thus babies with NPHV who have MINOR clinical signs do not appear to benefit from PPET. These children could benefit from additional educational programmes in later life.

The question of whether babies with NPHV and MAJOR clinical signs require PPET is not addressed or answered by this study. Further research needs to be done in this regard. It is also extremely difficult to categorise NPHV babies into the two proposed clinical gradings. Clearly, the disease is a dynamic one and severe signs may not be apparent immediately after birth. These may only appear later and be of such severity that the baby may succumb. There is no absolutely safe regime to follow but the following is suggested for those babies with MINOR or no apparent clinical signs.

## 3.1 MANAGEMENT OF NPHV WITH MINOR SIGNS

The babies should be nursed in an environment where regular care can be provided (e.g. intensive or special care).

Fluid balance should be maintained by intravenous infusion of 10% dextrose water. Weight, serum osmolality, urine volume and specific gravity should be monitored so that haemoconcentration does not occur.

Enteral feeding should be delayed until gastrointestinal function is established (bowel sounds, passage of meconium, etc). It is suggested that feeding be delayed for 24-36 hours.

The blood glucose should be monitored 3 hourly for the first 24-36 hours of life.

Watch for the presence of clinical signs. It is recommended that any baby with MAJOR signs be treated with PPET without delay.

## 3.2. PARTIAL PLASMA EXCHANGE TRANSFUSION

The usual method used for PPET should be re-evaluated in view of our current understanding of both fetal circulation and the placement of the catheter tip. Theoretically, a catheter inserted via the umbilical vein may be positioned near or in the portal vein. The withdrawal of the baby's blood is not seen as a problem, but the infusion of fresh plasma (or any other solution) may cause harm (Touloukain et al, 1973). The infusion pressure may exceed that in the portal vein, resulting in gastrointestinal capillary stasis or even reversal of flow. This may severely compromise the bowel wall and lead to NEC.

It is proposed that an alternative method of PPET be considered. A peripheral scalp or arm vein infusion could be utilised to administer the plasma so that the fluid eventually enters the right atrium and is well diluted in the large vessels before it reaches the bowel. The plasma should be allowed to run into the vein as fast as the infusion needle will permit. A polyvinyl catheter should be inserted into the umbilical vein until free flow of blood is obtained. As 5-10 ml aliquots of plasma are infused peripherally, so 5-10 ml of blood should be withdrawn from the umbilical vein. The infusion and withdrawal of fluid should be done concurrently. This method has been tried on several occasions and found to be effective. It is hoped that the incidence of NEC and other gastrointestinal signs will decrease if this method is adopted.

## CHAPTER 3 : THE FUTURE

Many problems related to NPHV remain unresolved. Some of the most important issues are to determine the causes of polycythaemia and hyperviscosity, to accurately diagnose the conditions and to be able to offer the most appropriate management for individual cases. Further research needs to be undertaken with a view to resolving some of these issues.

The aetiology of NPHV needs to be clarified. Methods need to be found so that the cause of NPHV in individual babies can be determined. The use of the recently described radioimmunoassay for erythropoietin could be profitably used to this end. Hopefully, markers can be found which could differentiate transfusion related NPHV infants from those whose condition has resulted from chronic intrauterine hypoxia. This differentiation might categorise those infants more at risk of developing serious clinical signs so that early treatment could be initiated.

Improved guidelines for the identification of those infants who are more likely to have life-threatening complications of NPHV are required. The division of clinical signs into MINOR and MAJOR in this thesis is offered as a guide in this regard. However, further research into the assessment of this classification of clinical signs and its application to all infants with NPHV needs to be undertaken. Alternatively, another assessment such as relationship between the level of the Hct and the presence of clinical signs may be a more sensitive predictor of the ultimate prognosis in these infants.

If treatment of babies with NPHV is found to be necessary, the method of the procedure should be revised. The proposal that the plasma be administered peripherally while blood is withdrawn from the umbilical vein should be researched.

Since babies with NPHV have been shown to have interactive problems, additional efforts should be directed towards ensuring that bonding between mother and infant is facilitated.

The haemodynamic aspects of blood flow, particularly of cerebral blood flow, require very careful study. Aspects such as the regulation of blood flow, oxygen utilization at a cellular level and variations of flow to different regions of the brain in babies with NPHV, need to be examined. It is hoped that the pursuit of these questions will result in further insight into the most appropriate methods of handling babies with NPHV.

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# APPENDIX

## INSTRUMENTATION

### VISCOSITY

The instrument used to measure whole blood viscosity in this study was the Wells-Brookfield Micro Viscometer Model LTV.

The instrument consists of several sub-assemblies linked in such a way that the the torque generated by a motor driven rotating cone in a blood sample is reflected by a pointer on a dial. At the top of the instrument an electronic motor (1) and gear transmission (2) are housed in a metal case (Figure 1). The motor can be made to run at various speeds (0.3, 0.6, 1.5, 3, 6, 12, 30 and 60 r.p.m.) by setting the speed selector (3). The motor can be disengaged from the rest of the instrument by a clutch lever (4). The rotating motor causes a calibrated dial (5) to turn according to the speed selected. The motor also drives a pivot shaft (6) via a spring (7). The arrangement is such, that the motor and dial are attached to one end of the spring while a pointer (8) and the pivoted shaft are attached to the other end. The shaft is linked, via a sapphire jewel (9), to a cone (10) which rotates in the water heated cup containing the blood sample. The resistance or viscous forces within the sample are transmitted to the pointer via the spring. The resistance or shear stress within the blood causes the pointer to deflect on the dial. This deflection will vary according to the speed (shear rate) at which the instrument is rotating. The dial reading value is multiplied by a factor (Table I) to give the viscosity value (units are centepoise or cps).

FIGURE 1

LINE DIAGRAM OF VISCOMETER SHOWING RELATIONSHIP OF MOTOR, DIAL, SPINDLE AND CUP HOUSING

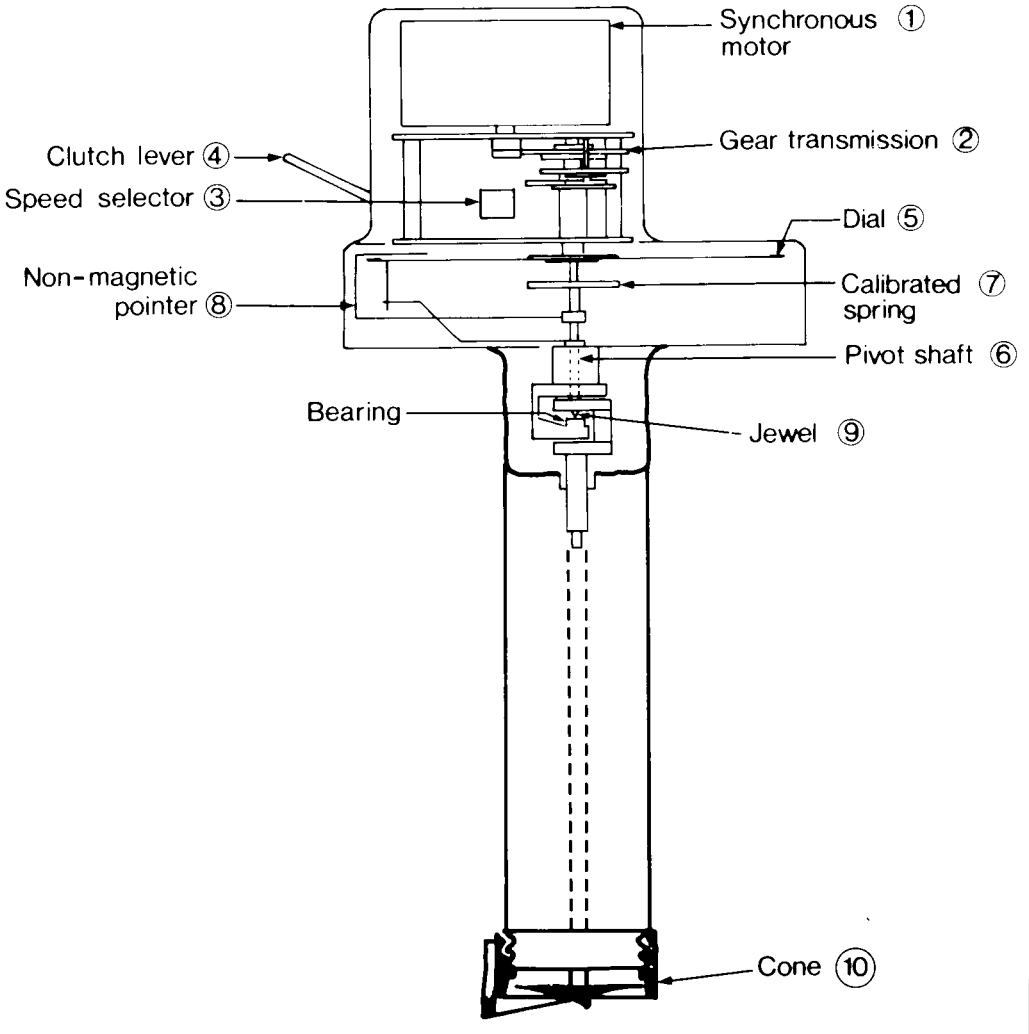


Fig. 1. Line diagram of viscometer showing relationship of motor, dial, spindle, and cup housing.

TABLE 1

VISCOMETER RATE (rpm), EQUIVALENT SHEAR RATE AND MULTIPLICATION FACTOR TO CONVERT DIAL READING TO CENTEPOISE

| r.p.m. | SHEAR RATE | FACTOR |
|---|---|---|
| 60 | 230 | 10 |
| 30 | 115 | 20 |
| 12 | 46 | 50 |
| 6 | 23 | 100 |
| 3 | 11,5 | 200 |

GEOMETRY

Cone and plate viscosity geometry are derived from standard calculations of shear stress and shear rate. The cone is fixed perpendicularly and is in point contact with a plate on which it rotates (Figure 2). The angle of the cone is obtuse ( $\theta$ less than 4°). The cone is rotated at a constant speed (W).

Viscosity (cps) is given by the ratio of shear stress to shear rate. The shear stress (Figure 3) is related to the sum of the torque (T) imparted by the blood sample on the cone. The shear rate is related to the speed of rotation (W), the gap width (C) and the radial distance (r) from the cone centre. Thus the mathematical relationships are:

FIGURE 2

DETAILS OF VISCOMETER CONE AND PLATE ARRANGEMENT

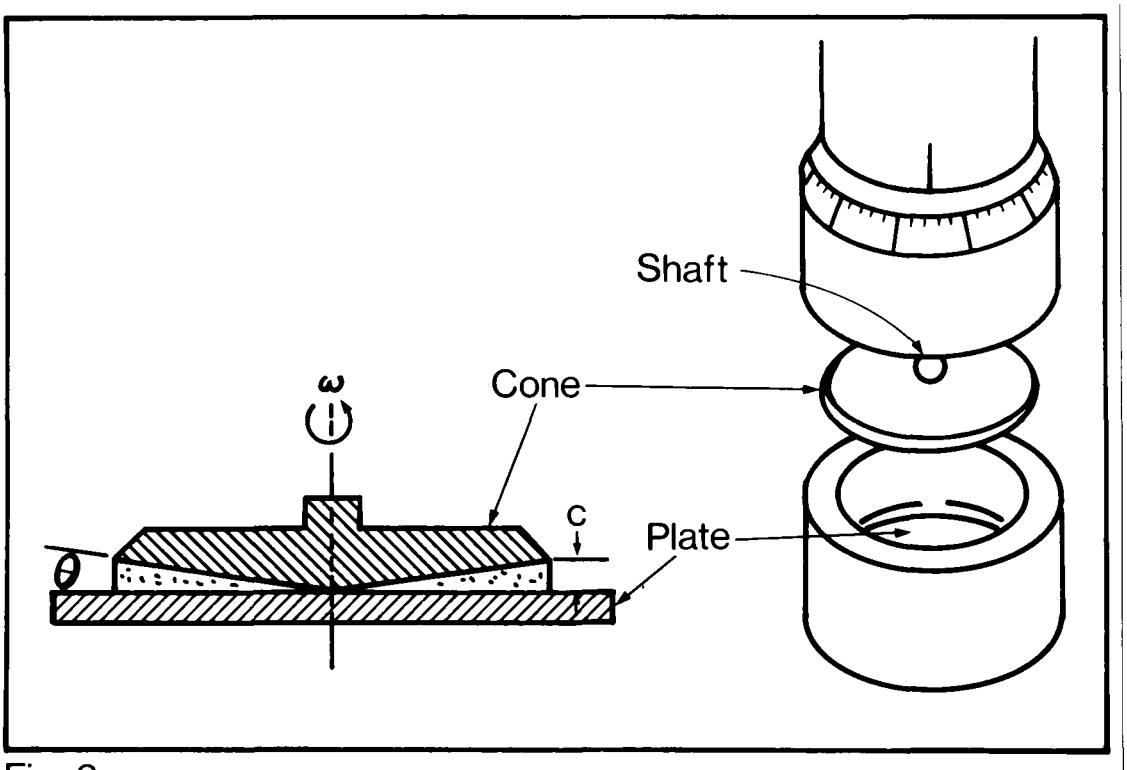


Fig. 2

FIGURE 3

GEOMETRY OF THE VISCOMETER CONE AND PLATE

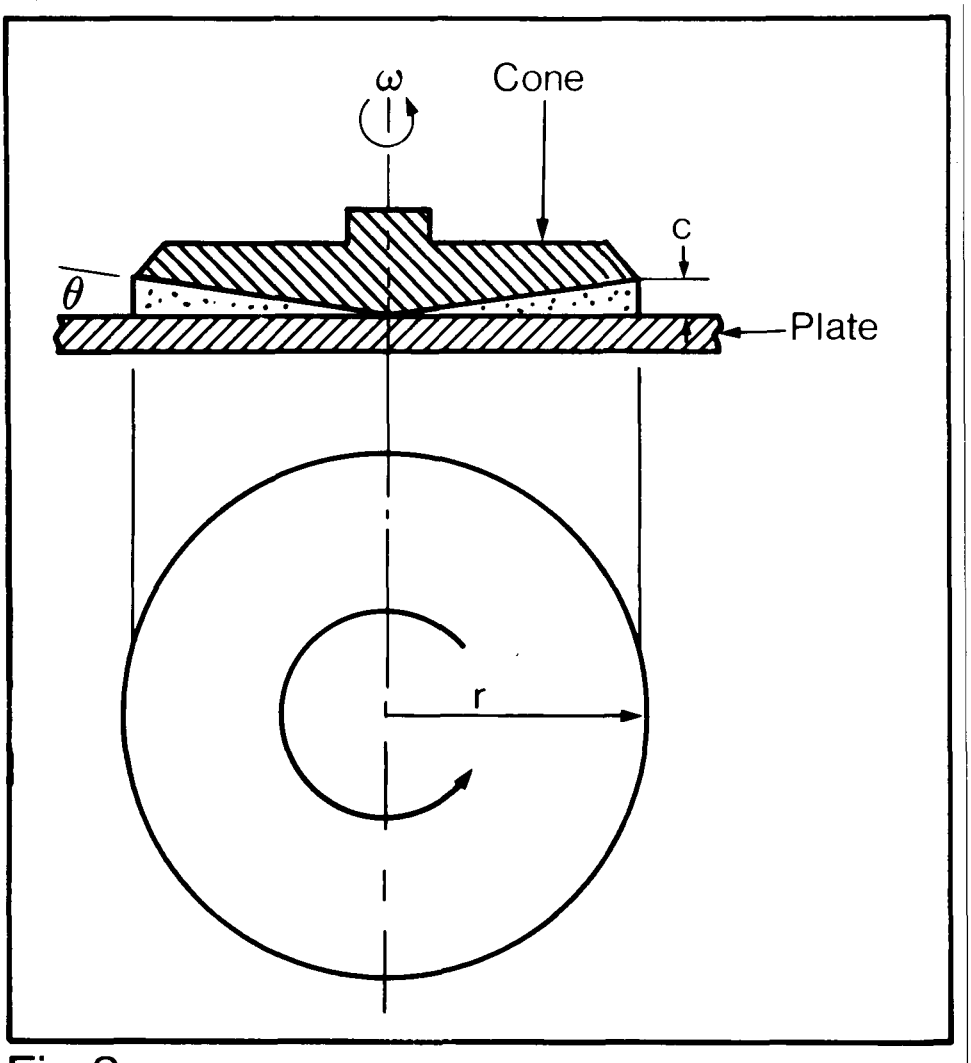


Fig. 3

$$\text{Shear stress (dynes/cm}^2) = \frac{T}{2/3\ \pi\ r^3}$$

$$\text{Shear rate (sec}^{-1}) = \frac{W}{\text{Sin}\ \Theta}$$

$$\text{Viscosity (cps)} = \frac{\text{Shear stress x 100}}{\text{Shear rate}}$$

Where $T$ = % full scale torque (dyne - cm)

$r$ = cone radious (cm)

$W$ = cone speed (rad/sec)

$\Theta$ = cone angle (degrees)

INSTRUMENT QUALITY CONTROL

MICROVISCOMETER

1. Reproducibility

Two standard oils of viscosity 50 and 5 cps were tested repeatedly and alternately in the viscometer. This test was repeated 15 times i.e. 30 samples. There was no statistical difference ($p = 0,2$) between successive paired readings. The instrument thus reproduced a very similar result repeatedly.

2. Accuracy

The two standard oils of known viscosity were again tested repeatedly. The instrument read an average of 0,35 cps (range 0 - 1,5 cps) less than the stated value and 0,38 cps (range 0-1,1

cps) greater than the standard value over 30 trials. The standard deviation of values obtained for oil at 50 cps was 0,046 cps and that for oil at 5 cps was 0,25 cps. The instrument was thus considered to be accurate.

MICROCENTRIFUGE

The microcentrifuge used was a Clements (H.I. Clements Pty Ltd, Sydney, Australia) which spun at 1200 rpm. Each fresh blood sample was repeatedly tested 30 times, using the method employed for the study.

The mean value was 42,7%, SD 0,69%, SEM 0,13%. It was therefore concluded that the method was reproducible. The greatest variation about the mean was 1%. Thus the laboratory methods for determining the Hct were reproducible.

ERYTHROPOIETIN

The method used was the Haemagglutination-Inhibition Assay for Erythropoietin (JCL Clinical Research Co. Knoxville, Tennessee). The test was used in this study in an attempt to identify babies who had polycythaemia as a result of excessive erythropoietin and those who did not. The results of the erythropoietin assay are shown in Table 2. Results of babies who had what were considered to be normal values, those with elevated levels and those babies where no results were available are shown. Analysis using both Chi squared and Fisher's Exact test were not significant.

The data was not included in the main text because there was some concern about the accuracy of the method and about what was

# THESIS DATA

Details of the patient data for this thesis are available upon request from the author. Should this information be required it will be supplied from the Department of Paediatrics and Child Health, University of Cape Town.

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