SOME PROPERTIES OF HUMAN FETAL AND MATERNAL BLOOD

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The differences between the bloods of pregnant animals and of their fetuses, particularly in regard to the properties of the hemoglobin, have interested workers for many years. However, the results of different workers are in conflict on several points, perhaps because of species differences, or of varying conditions for obtaining blood or differing methods of calculation.

The earliest evidence of difference between fetal and maternal hemoglobin was the greater resistance to alkaline denaturation observed in the fetal hemoglobin (1, 2, 3). These workers calculated that adult blood contained up to 20 per cent of the alkaline-resistant hemoglobin, whereas fetal blood consisted almost wholly of the resistant type. Differences in crystal structure (2, 3) have added to the evidence for difference in the hemoglobins.

The property of fetal and maternal blood on which the greatest amount of work has been done is the oxygen affinity. This property is usually described by an oxygen dissociation curve which presents graphically the amount of oxygen bound to hemoglobin through a range of oxygen pressures. Plotted on the usual arithmetic coordinates with oxygen pressures as abscissae and % HbO_2 as ordinates, the curve has the well known S-shape. The shape of the curve has been found to be quite constant among adult animals of a given species but to vary considerably from species to species. It has been noted that various conditions displace the curve to right or left without changing the fundamental shape. Among these the most important is the pH. In a more acid medium the hemoglobin has less affinity for oxygen at all pressures and its curve is therefore shifted to the right; conversely, a more alkaline reaction shifts it to the left.

The oxygen dissociation curve is frequently plotted on a logarithmic scale, in which case the characteristics of shape and lateral displacement are more easily dissociated. Plotting $\log \frac{100\ Hb}{HbO_2}$ against $\log pO_2$, the curve has been found to approximate a straight line, the slope of which has the same significance as the shape observed in the arithmetic curve and of which the intercept of either axis measures the lateral displacement. The Hill-Barcroft empirical equation describes mathematically this type of relationship; so, from the logarithmic graph of a given blood the constants of the equation can be easily determined and used to describe the characteristics of the dissociation curve. The usual form of the equation is

$$y = 100\left(\frac{Kx^n}{1 + Kx^n}\right)$$

where $y =$ % HbO_2, $x = pO_2$ and K and n are constants. Transforming this equation into the units of the logarithmic graph, one obtains:

$$\log \frac{100\ Hb}{HbO_2} = -n \log x - \log K + 2.$$

From this it will be seen that the slope of the graph is $-n$ and that K is easily calculated from any one point (*e.g.* $Hb = HbO_2$).

With this brief discussion as a background, we may review the evidence in the literature on the comparison of the oxygen dissociation curves of fetal and maternal hemoglobin. Among the first investigations was Huggett's demonstration (4) that diffusion alone accounts for the gas transfer across the placenta in the goat. Incidentally, it appeared from his data that the fetal curve lay to the right of the maternal, *i.e.*, at any tension the fetal blood combined with less oxygen than the maternal. This rather unfavorable physiological situation has not been confirmed in any species of animal. In fact, almost all investigations on humans (5, 6, 7) have found the opposite to be true, namely that the fetal oxygen disso-

ciation curve lay to the left of the maternal. Since Haselhorst and Stromberger worked with curves constructed from a single point according to the Hill-Barcroft equation, nothing could be said about differences in the shape of the curve. However, Eastman *et al.* found a different shape in the fetal blood curve in all their cases and Leibson *et al.* found a characteristic shape to the fetal blood curves in several of theirs. The difference in shape consisted in a greater shift to the left in the lower range than in the upper. On the other hand, Noguchi (8) constructed his curves on a logarithmic scale to determine the constants of the Hill-Barcroft equation, and concluded that the constant "*n*," which measures the slope of the logarithmic curve, had similar values in fetal and normal bloods.

Among the other animals studied have been the goat (9, 10), the rabbit (10), the chick (11), and the calf (12). In all, the curve for fetal blood was found to lie to the left of that of pregnant and non-pregnant adult animals. In the goat (9) it had an abnormal shape as well as a general displacement to the left. Furthermore, both these changes were found to be similar in buffered hemoglobin solutions (13). The latter finding is in contrast to the paradoxical report by Haurowitz (3) that the curve was shifted to the right for solutions of human fetal hemoglobin but to the left for cells suspended in saline or plasma. Apparently this paradox has not been confirmed.

Differences between blood of pregnant and non-pregnant animals have in almost all cases been observed as small and attributable to differences in pH. Frequently the curves were obtained at a constant pCO_2 (*e.g.* 40 mm. Hg) in the equilibrating gas. Under this condition the pH of two bloods will approximate the same standard only provided the buffer power (*i.e.* the bicarbonate) of the bloods is equal. For example, the blood of a pregnant animal with a lower bicarbonate will be more acid at constant pCO_2 than that of the non-pregnant animal used for comparison. Measured at constant pCO_2, according to Leibson *et al.* (7), the human maternal curve is to the right of the non-pregnant normal; calculated to constant pH, they found the maternal curves lay slightly to the left. Other workers have calculated their curves either at constant pCO_2 or at the pCO_2 of the blood as taken. It is impossible from their data to recalculate their curves to a given hydrogen ion concentration. Whereas it is the consensus of opinion that deviations in the maternal curves are attributable to differences in pH, the considerable magnitude of the shift in fetal blood has been taken to indicate the existence of a special fetal type of hemoglobin.

The primary purpose of this work is to acquire sufficient data on the bloods of non-pregnant and of pregnant women and of the fetuses at term to determine the complete oxygen dissociation curves at constant pH. The importance of choosing a standard pH rather than a standard pCO_2 is apparent from the previous discussion, especially in order to investigate the fundamental question of a special fetal hemoglobin. To correct our curves to constant pH it was necessary to measure the bicarbonate content, calculate the pH, and establish the degree of shift in the oxygen dissociation curve with changes in pH. Likewise, because of the conditions of labor and anesthesia, the blood lactic acid values were determined in order to be able to extrapolate the acid-base conditions back to the period before the onset of labor.

Since Barcroft (9) has emphasized that in goats the fetal type of hemoglobin is most pronounced at eighteen weeks of gestation and has disappeared at birth or soon thereafter, we have attempted to determine curves of human blood before and after the normal ninth month of development. To do this we obtained bloods of infants born prematurely, and in two instances of infants born at term we obtained bloods periodically throughout the first month of life. So that changes might similarly be plotted for the mother, maternal bloods were studied throughout the last half of pregnancy.

In so far as sufficient blood was available, determinations of sodium, chloride, total base and total nitrogen were made on the serum. In this way a gross electrolyte change could be detected if it were sufficient to cause shift in the oxygen dissociation curve.

It is hoped that the sum total of evidence can be integrated to answer the remaining questions regarding the properties of so-called fetal hemoglobin and also to quantitate the possible advan-

tages arising from differences between maternal and fetal blood for gas exchange between mother and fetus.

METHODS

Venous blood samples were obtained on thirteen pregnant women, seven of them between the fourth and eighth month of pregnancy, six of them within twelve hours before delivery. Eight blood samples were taken from the umbilical cord of infants born at term, in each case the blood being obtained within fifteen minutes of tying off the cord. Similar blood samples were obtained from the cords of two premature infants. On two of the infants born at term, repeated blood samples were taken from the jugular vein during the first month of life. Venous blood samples were also obtained from six normal non-pregnant women, since, as far as we could discover, the standard oxygen dissociation curves reported in the literature are all on men's blood.

Because of the known variability in gas content of cord blood obtained at birth, no gas analyses of the bloods as drawn were made. The blood in each case was mixed with heparin (Connaught Laboratories, Toronto), covered with heavy mineral oil to prevent evaporation, and immediately chilled in ice. All equilibrations and gas analyses were made as soon as possible, the blood being kept packed in ice except at times of equilibration. When the patient had received ether anesthesia, the ether was removed from the blood by equilibrating it with room air for fifteen minutes at 25°.

The technique of determining the oxygen dissociation curve and the CO_2 capacity at a pCO_2 of 40 mm. Hg (T_{40}) was essentially that described in detail by Dill *et al* (14). The following changes in the procedure were made: The CO_2 pressure in the tonometers was set at 30 or 35 mm. Hg because it was expected that the bicarbonate content of these bloods was lower than normal. In this way we hoped to have the pH as near 7.40 as possible, to which figure the curves were finally corrected as in the original technique

$$\left(\frac{\Delta \log pO_2}{\Delta pH} = -0.479\right).$$

The oxygen pressures were set at 5, 10, 20, 35, 50, 70 and 200 mm. Hg in order to cover a wider range than desired in the original technique. In addition, one or two points were determined in the approximate range of 50 per cent oxygen saturation at pressures of CO_2 of 20 and 80 mm. Hg. These points served to determine the shift in the curve with pH.

Lactic acid determinations (Edwards' modification of Friedmann, Cotonio, and Shaffer (15)) were made on all blood samples immediately before the final equilibration. The percentage of red cells in the original blood was measured by hematocrit. Serum was analyzed for sodium according to Consolazio and Dill (16), chloride according to the method outlined in Peters and Van Slyke (17), total base by the method of Consolazio and Talbott (18), and total nitrogen by the micro Kjeldahl method (Keys' modification (19)).

The oxygen dissociation curves at $pH_s = 7.40$ were plotted in the usual arithmetical coordinates and also on logarithmic coordinates

$$\left(\log pO_2 \text{ against } \log \frac{100\ Hb}{HbO_2}\right).$$

The latter method gives an approximate straight line, the slope of which is the constant "*n*" in the Hill-Barcroft equation. The axis intercept defines "*K*" in the same formula. These two constants were determined for each blood.

For comparison with data in the literature, and for evaluating *in vitro* conditions, the midpoint of each curve ($Hb = HbO_2$) was also calculated at $pCO_2 = 40$, using the line charts of Henderson (20) and of Dill *et al.* (14) for the conversion.

With the value for T_{40} of the blood as measured and the blood lactate, it was possible to determine an extrapolated T_{40} representing the value if the lactate were 10 mgm. per cent and presenting the probable picture before the onset of labor and anesthesia. To make this calculation, use was made of the fact that lactic acid displaces bicarbonate in equimolecular amounts at the same pH. The steps in the conversion were:

(*1*) Calculation of pH_s at the T_{40} point in the blood as studied.

(*2*) Adding to the measured T_{40} value an increment equivalent to the excess lactate above 10 mgm. per cent.

(*3*) The pH_s from (*1*) and the total CO_2 from (*2*) determine one point on the CO_2 dissociation curve of the blood in its original state; the pCO_2 of this point was determined from the line chart of Peters and Van Slyke (17).

(*4*) The T_{40} value of the new curve was read off from the Henderson line chart (20).

RESULTS

The mean and total range of values of the oxygen dissociation curves between 10 and 90 per cent saturation of the three groups of bloods (non-pregnant, maternal and fetal) are presented in Figure 1, all curves being corrected to pH_s 7.40. The striking feature to be observed is the position of the fetal curves: these lie to the left of both the normal and the maternal. The sole point where the curves overlap is near 90 per cent, where the technical difficulties of accurate measurement are greatest. In spite of the shift, however, inspection fails to show any striking difference in the shape of the different groups of curves.

In the same chart, comparison of the curves on the pregnant and the non-pregnant women shows that, whereas the range of the two groups

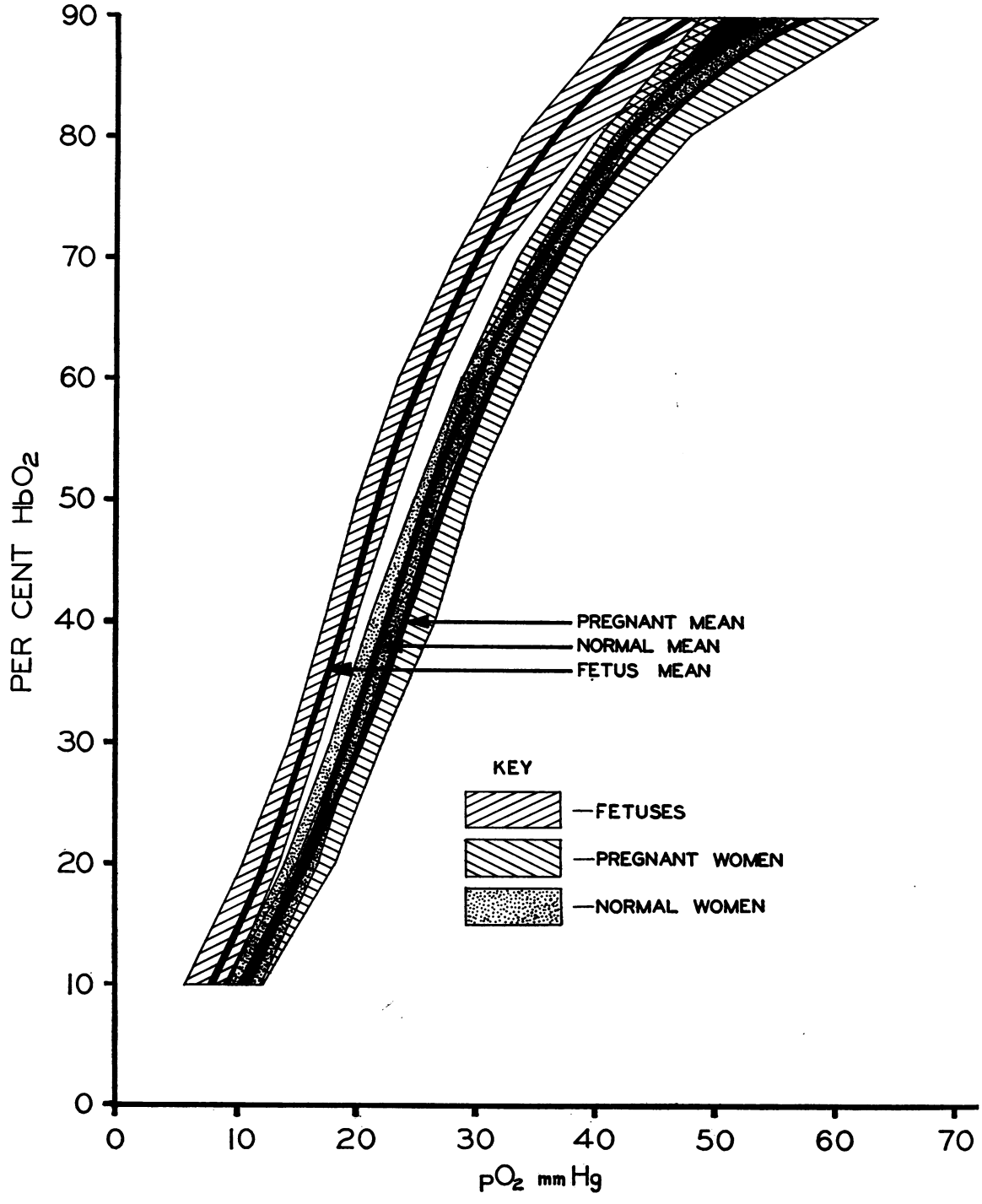

FIG. 1. MEANS AND RANGES OF OXYGEN DISSOCIATION CURVES

overlaps throughout, most of the maternal curves lie to the right and none to the left of the range of the non-pregnant women. The mean position for the dissociation curves on the blood of pregnant women lies slightly to the right of that of the non-pregnant.

The range and mean values of the control series of normal women shown here correspond fairly

well to the standard established from the blood of normal men (21). The mid-positions (Hb $= HbO_2$) agree almost exactly (men $= 26.3$ mm. Hg; women $= 26.0$ mm. Hg). There would seem to be a slightly more sharp S-shape to the women's curve, as can be appreciated from Table I of the comparative pressures of oxygen necessary for different degrees of saturation of the hemoglobin.

TABLE I

Comparison of oxygen dissociation curves of normal men and women at $pH_s = 7.40$

% HbO_2	pO_2 (*mm. Hg*) Normal men (Dill, Edwards and Consolazio)	Normal women (mean of 6) (This paper)
10	8.2	10.5
20	13.4	15.3
30	17.9	19.2
40	22.0	22.6
50	26.3	26.0
60	31.1	30.2
70	36.1	35.6
80	45.7	42.2
90	61.4	54.1

Table II presents the figures for one point on each of the curves obtained (column 2), together with other data on each blood sample. The figures in column 2 confirm the visual impression gained from the chart, namely, that fetal curves are significantly and uniformly shifted to the left and that, while the mean maternal curve lies somewhat to the right of normal, this difference is of doubtful statistical significance. The difference between the curves on the blood of pregnant and non-pregnant women appears more striking if it is noted that the range of the mid-position of the curves on the six non-pregnant women is 24.9 to 26.8 mm. Hg and that nine out of thirteen of the maternal bloods lie outside this range to the right.

The first column labelled T_{40} gives a measure of the alkali reserve in each case. It should be noted that corrections have been made whenever the lactic acid was elevated above 10 mgm. per cent, so that changes in these values are not merely temporary effects of lactic acid. The well-known progressive decrease in alkali reserve during pregnancy is again demonstrated by a comparison of the pre-term with the term groups of maternal bloods. The more marked diminution in bicarbonate in the fetal bloods is not so generally known and is the opposite of the findings in goat fetuses (22).

Figures in the third column are calculated values of the pO_2 for half saturation of the blood at standard pCO_2. In this case the different bicarbonate values modify to some degree the relations observed at constant pH, since at constant pCO_2 the bloods with the lower bicarbonate are more acid. The shift of the fetal blood curves to the left is still present but less marked; on the other hand, the maternal curves under these conditions are seen to be definitely shifted to the right.

The constants from the Hill-Barcroft equation were measured from logarithmic graphs of each curve and are presented in the fourth and fifth columns. In each case the curve approximated a straight line, the slope of which is "*n*." Our data indicate that "*n*" is not significantly different in the various groups. This constancy of "*n*" confirms our visual impression from the arithmetic curves that all were approximately the same shape. The "*K*" values are a measure of the position of the curve; they have the same significance as oxygen pressures for half saturation. Expressed for the sake of convenience as negative logarithms, they will be seen in the fifth column to parallel the oxygen pressures at half saturation in column 2.

The values for cell volume and HbO_2 capacity demonstrate anew the tendency to moderate anemia in pregnancy and the frequent polycythemia of newborn infants.

The last column shows the calculation of the factor $\frac{\Delta \log pO_2}{\Delta pH}$, which measures the shift in the logarithmic curve with pH. The importance of this measurement is two-fold: (*1*) If it differs in fetal or maternal blood from the standard established for normal man it would further establish a fundamental difference in the hemoglobin. (*2*) Since the oxygen dissociation curves were corrected to constant pH, using the factor for normal man, it is necessary to measure this factor in the bloods studied in order to be sure of the validity of the corrections made. Actually the factor was measured on the logarithmic curve from the equilibrium points taken at high or low CO_2 pressures. While there is some scatter in the individual values for these factors, it is evi-

TABLE II

Oxygen and carbon dioxide affinity of bloods of non-pregnant and pregnant women and of fetal blood at birth

Non-pregnant women		T_{40} corrected to normal lactate	pO_2 at 50 per cent oxygen saturation		Hill-Barcroft formula constants		Cell volume	HbO_2 capacity	$\frac{\Delta \log pO_2}{\Delta pH}$
			$pH_s = 7.40$	$pCO_2 = 40$	n	$-\log K$			
		volume per cent	*mm. Hg*				*per cent*	*volume per cent*	
Ca		48.7	26.4	25.5	2.72	3.86	42.3	18.02	
Ja		49.9	26.8	25.9	2.61	3.72		17.02	
Te		42.7	24.9	25.2	2.61	3.64	43.7	19.61	
Co		48.5	26.5	25.8	2.78	3.96	38.1	16.47	
Na		45.8	25.8	26.2	2.63	3.71	45.4	17.37	
Se		44.6	25.8	26.6	2.53	3.57	40.3	16.82	
Mean		46.70	26.03	25.87	2.647	3.743	41.96	17.55	
σM		1.14	0.28	0.21	0.037	0.059	1.28	0.465	
Pregnant women									
Pre-term	Month of pregnancy								
Ku	4	43.8	25.8	26.6	2.78	3.92	38.5	16.63	−0.53
Br	5	43.7	29.4	30.8	2.50	3.67	33.8	15.00	−0.48
Co	5	45.4	28.2	28.5	2.68	3.87	31.4	15.78	−0.45
O'B	5½	43.5	25.9	26.9	2.76	3.89	33.9	14.25	−0.47
Gr	7½	42.6	27.6	29.0	2.52	3.64	37.2	16.13	−0.38
Co	8	45.0	28.7	29.5	2.52	3.67	31.1	13.67	−0.50
Ma	8½	47.7	29.5	29.2	2.72	4.00	37.9	16.06	
Mean		44.53	27.87	28.64	2.640	3.809	34.83	15.36	−0.469
σM		0.64	0.58	0.56	0.046	0.055	1.16	0.411	0.020
Term									
Ba		41.4	26.1	27.9	2.59	3.67	37.4	15.98	−0.50
Fl		40.3	26.5	29.1	2.50	3.56	36.8	16.70	−0.45
Hi		36.0	27.0	30.1	2.79	3.99	30.4	15.50	
Po		41.8	27.0	28.5	2.50	3.58	41.1	16.97	−0.49
McG		47.0	27.8	27.8	2.48	3.58	36.3	15.41	−0.47
An		39.7	29.2	31.1	2.72	3.97	35.9	17.40	−0.56
Mean		41.03	27.27	29.08	2.597	3.725	36.32	16.33	−0.494
σM		1.46	0.45	0.53	0.053	0.082	1.41	0.334	0.016
Mean of all pregnant		42.92	27.59	28.85	2.620	3.770	35.52	15.81	−0.480
σM		0.88	0.37	0.38	0.034	0.047	0.88	0.294	0.014
Fetus Term									
Fl		35.9	22.3	24.3	2.51	3.38		22.68	
Hi		38.0	21.6	23.2	2.35	3.13	51.1	19.81	−0.40
Po		35.6	20.9	22.8	2.54	3.35	50.6	22.46	−0.52
McG		34.5	23.2	25.6	2.49	3.40	57.6	24.53	−0.52
An		31.1	22.0	25.4	2.60	3.49	59.6	25.40	−0.49
Ro		33.4	20.0	22.3	2.50	3.25	60.0	24.36	−0.52
Wh		33.5	21.4	23.7	2.72	3.62	59.2	25.61	
Bo		37.6	21.9	24.2	2.59	3.47	44.5	18.15	
Premature									
Ma (7th month)		40.4	22.4	23.4	2.70	3.64	43.1	20.46	−0.57
Pa (5th month)		30.9	22.9	27.3	2.69	3.65	49.9	20.63	−0.47
Mean		35.09	21.86	23.94	2.569	3.438	52.84	22.41	−0.499
σM		0.96	0.30	0.42	0.036	0.054	2.18	0.813	0.020

dent that there is no significant deviation in the mean values either between the different groups or between any of them and the value of —0.48 which has been found for the blood of normal men (14).

The data on the two premature infants are remarkable only for the lack of differentiation from the term infants. The oxygen dissociation curves are well within the range observed on infants at term. As expected, neither of them showed polycythemia, which from available data seems to be a development of the last two months of fetal life (23).

Table III presents the results of some analyses on the sera of these bloods. The bicarbonate values at the arbitrary pCO_2 of 40 are calculated from the CO_2 content of the whole blood equilibrated at a known pCO_2 according to Peters and and Van Slyke. It is obvious that no anion-cation balance sheet can be made since the bicarbonate values are taken at arbitrary conditions and not those *in vivo*. From the point of view of the possible effect of salt concentration on the oxygen dissociation curve, it can be concluded, however, that changes in the serum are too small to explain the shift in the fetal oxygen dissociation curve. The changes in some of the separate ionic concentrations, however, are of interest. A tendency to a high chloride content, especially in the fetal bloods, is associated with a low bicarbonate concentration.

TABLE III

Analyses of serum of pregnant women and fetuses at birth

Pregnant women		Sodium	Chloride	Total base	HCO_3^- at $pCO_2=40$	Total nitrogen
Pre-term	Month of pregnancy	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*m. Eq. per liter*	*grams per liter*
Ku	4	138.2	106.3		22.7	11.18
Br	5	136.1	108.7		22.5	10.41
Co	5	135.6	107.2		23.3	11.06
O'B	5½	135.6	106.9		22.0	11.30
Gr	7½		100.1		22.1	11.41
Co	8	135.1	103.6		22.6	10.53
Ma	8½	140.0	103.3		24.8	
Term						
Ba			105.2		21.4	10.43
Fl		136.1	110.3		22.4	11.02
Hi			103.7		18.3	10.90
Po			106.7		21.9	10.72
McG		140.9	108.2	154.2	24.2	9.98
An		140.2	109.5		20.8	10.06
Fetus Term						
Fl			111.3		20.4	11.34
Hi		139.8	108.1		20.6	
Po		130.9	104.2		20.0	10.32
McG		129.1	107.4	157.0	19.9	9.47
An			104.1		18.2	10.58
Ro		127.3	103.9		19.3	11.17
Wh		136.8	110.9		19.7	9.26
Bo		136.1	112.9	154.3	19.9	7.55
Premature						
Ma (7th month)		126.8	109.5		22.2	8.44
Pa (5th month)		125.1	113.6	135.7	16.9	6.07

TABLE IV

Changes in blood during the first month of life

Subject	Age	T_{40} corrected to normal lactate	pO_2 at 50 per cent saturation		Cell volume	HbO_2 capacity
			$pH_s=7.40$	$pCO_2=40$		
		volume per cent	*mm. Hg*		*per cent*	*volume per cent*
Wh	Birth	33.5	21.4	23.7	59.2	25.61
	1 day	42.0	22.2	22.7	49.3	21.85
	5 days	42.2	23.3	23.8	43.1	20.21
	34 days	41.7	27.7	29.2		17.90
Bo	Birth	37.6	21.9	24.2	44.5	18.15
	3 days	39.0	23.0	24.1	53.4	23.15
	34 days	49.7	25.1	24.3	35.5	14.83

The most striking abnormalities are seen in the two bloods of prematurely born infants. In both, the serum sodium is definitely low; this finding is shared by two of the term infants but by no others. Even more remarkably low is the total base value for one of the premature infants. However, this value is normal for two term infants and one pregnant woman on whom the determination was carried out. Likewise, in the two premature infants' blood, the serum nitrogen (a measure of serum protein) is definitely lowered. The significance of these chemical changes is not known and their finding may be considered incidental to the present work. It is of interest to speculate, however, on whether such chemical deficiencies may not be significant physiological handicaps to premature infants.

Table IV presents the data on two infants whose blood was tested throughout the first month of life. It will be seen from the progressive increase in the figures of the midpoints of the oxygen dissociation curves that the curves at constant pH_s shifted gradually to the right so that they were within the normal range at thirty days

of age. Concomitantly, there was a rise in bicarbonate and a fall in HbO_2 capacity. The effect of the former is to make the change in the oxygen dissociation curve at constant pCO_2 less striking than at constant pH_s, as the third column in the table indicates. This is due to the fact that, as measured at constant pCO_2, the blood becomes increasingly alkaline as the bicarbonate rises.

DISCUSSION

The significance of the observed characteristics of fetal, maternal, and normal blood may be discussed profitably from two points of view. In the first place, there is the theoretical question of a chemically different hemoglobin in the fetus. The second point of view is the physiological, according to which we may inquire into the advantages or disadvantages to the fetus of the different properties which its blood displays.

The data presented show that the fetal blood has a greater affinity for oxygen than the blood of pregnant and non-pregnant women over the entire range of oxygen pressures. These comparisons were made at the same pH of the serum. In order to be sure that the hemoglobins are inherently different, it would be necessary to compare them at the same environmental pH, namely that of the cell. Such values were not measured directly but they may be calculated from the values for the serum constituents, assuming normal permeability of the cell membrane. Thus from our data we may conclude that *if the cell membrane of the fetal red cell has the same characteristics of permeability as that of the adult cell, then the fetal hemoglobin has truly different properties.* Unfortunately we have no positive evidence by which we make this assumption of constant permeability. In fact, there is the evidence of Andreen-Svedberg (24) that calves' corpuscles are more permeable to glucose than cows' corpuscles, which gives a hint that cell membranes of young animals may differ from those of adults.

Thus the evidence for a chemically different human fetal hemoglobin is not clinched. That for goats is much surer, since the same differences were observed on buffered hemoglobin solutions at the same pH and also because the fetal curve was invariably found to have a different shape from the adult. Our evidence fails to confirm a characteristic fetal shape to the curve in humans, so one link in the evidence for a true human fetal hemoglobin is lacking. The final answer will await more knowledge of fetal red cell permeability and a further study of human hemoglobin solutions.

From the point of view of applied physiology the preceding considerations are less important. There can be no doubt that under the same serum conditions of pH the fetal blood will take up more oxygen in the placenta than would adult human blood. By the same token it will be able to give up less of its oxygen at the same oxygen tension in the fetal tissues. Since, however, it is established that fetal tissues use less oxygen per gram of weight than adult tissues (25), presumably due to the fact that heat loss is minimal *in utero,* the latter physiological disadvantage may not be important.

Granted that there seems to be a physiological advantage to the fetus provided the serum pH of mother and fetus is identical, we must next inquire as to how much this concept is actually modified by possible differences in the pH of the two bloods. The lowered bicarbonate in both mother and fetus tends to make the serum more acid than normal unless compensatory adjustments are made. In the case of the mother such compensatory regulation is brought about by the respiratory center, so that *in vivo* her blood approaches conditions of standard pH. The fetus, on the other hand, has no central respiratory control of acid-base balance; the pH of its serum is determined by a balance between the CO_2 removal through the placenta and the CO_2 given up by the tissues. Thus our figures for the fetal blood at constant pCO_2 approach more nearly those *in vivo* than do the figures at constant pH. As may be noted from Table II, a comparison of such figures (mother at pH 7.40, fetus at pCO_2 40) brings the fetal and maternal curves closer together. Unfortunately, accurate figures of the pCO_2 of the fetal blood in *utero* are not available. It is quite possible that the fetal pCO_2 *in vivo* is appreciably higher than 40 mm. Hg; in which case the fetal and maternal curves will be even closer together. Thus there are two opposing forces acting in the case of the fetal blood: an inherent greater affinity for oxygen facilitating the taking up of oxygen and a physiologically more acid state

opposing it. It is likely, however, that the former force is somewhat greater, so that the fetal blood operates at an advantage in becoming promptly saturated with oxygen in its passage through the placenta.

SUMMARY AND CONCLUSIONS

1. Blood was obtained from thirteen pregnant women, six non-pregnant women and eight human fetuses at term birth, and the oxygen dissociation curves, together with certain serum electrolytes, were determined.

2. The oxygen dissociation curve of fetal bloods at constant pH_s is displaced to the left compared with that of pregnant and non-pregnant women. This suggests but does not prove the existence of qualitatively distinctive fetal hemoglobin.

3. The mean oxygen dissociation curve of maternal blood shows only a doubtful deviation from that of the non-pregnant women, although more than one-half of the individual curves were displaced to the right.

4. The oxygen dissociation curves of two premature infants were not different from those of infants at term.

5. The oxygen dissociation curve after birth shifts to the right so that within thirty days it is like that of the normal adult.

6. The alkali reserve of fetal blood is markedly lowered; that of pregnant women moderately so. This difference makes it probable that the difference in oxygen curves is less marked *in vivo* than at constant pH_s.

7. The sera of the two premature infants, as well as those of two of the infants born at term, showed low serum sodium values.

BIBLIOGRAPHY

1. von Krüger, F., and Gerlach, W., Weitere Untersuchungen über den Einfluss von Blutentziehungen auf die Resistenz des Blütfarbstoffes. Ztschr. f. d. ges. exper. Med., 1927, **54**, 653.
2. Brinkman, R., Wildschut, A., and Wittermans, A., On the occurrence of two kinds of haemoglobin in normal human blood. J. Physiol., 1934, **80**, 377.
3. Haurowitz, F., Die Hämoglobine des Menschen. Hoppe-Seyl Ztschr. f. physiol. Chem., 1935, **232**, 125.
4. Huggett, A. St. G., Foetal blood-gas tensions and gas transfusion through the placenta of the goat. J. Physiol., 1927, **62**, 373.
5. Haselhorst, G., and Stromberger, K., Über den Gasgehalt des Nabelschnurblutes vor und nach der Geburt des Kindes und über den Gasaustausch in der Plazenta. Ztschr. f. Geburtsh. u. Gynäk., 1931, **100**, 48.
6. Eastman, N. J., Geiling, E. M. K., and De Lawder, A. M., Foetal blood studies. IV. The oxygen and carbon-dioxide dissociation curves of the foetal blood. Bull. Johns Hopkins Hosp., 1933, **53**, 246.
7. Leibson, R. H., Likhnitzky, I. I., and Sax, M. G., Oxygen transport of the foetal and maternal blood during pregnancy. J. Physiol., 1936, **87**, 97.
8. Noguchi, M., Oxygen dissociation curve of hemoglobin in the umbilical blood of the newborn. Japan J. Obst. and Gynec., 1937, **20**, 358.
9. Barcroft, J., and others, Conditions of foetal respiration in the goat. J. Physiol., 1934, **83**, 192.
10. Hall, F. G., A spectroscopic comparison of foetal and maternal blood of the rabbit and goat. J. Physiol., 1934, **82**, 33.
11. Hall, F. G., Haemoglobin function in the developing chick. J. Physiol., 1934, **83**, 222.
12. Roos, J., and Romijn, C., Some conditions of foetal respiration in the cow. J. Physiol., 1938, **92**, 249.
13. McCarthy, E. F., A comparison of foetal and maternal haemoglobins in the goat. J. Physiol., 1933, **80**, 206.
14. Dill, D. B., and others, Der Gasaustausch in den Lungen im Alter. Ztschr. f. Altersforsch., 1940, **2**, 20.
15. Edwards, H. T., A simplified estimation of lactate in normal human blood. J. Biol. Chem., 1938, **125**, 571.
16. Consolazio, W. V., and Dill, D. B., The determination of sodium. J. Biol. Chem., 1941, **137**, 587.
17. Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry. Vol. II, Methods. Williams and Wilkins Co., Baltimore, 1932.
18. Consolazio, W. V., and Talbott, J. H., The determination of total base in biological material by electrodialysis. J. Biol. Chem., 1940, **132**, 753.
19. Keys, A. B., A rapid micro-Kjeldahl method. J. Biol. Chem., 1940, **132**, 181.
20. Henderson, L. J., Blood. A Study in General Physiology. Yale University Press, New Haven, 1928.
21. Dill, D. B., Edwards, H. T., and Consolazio, W. V., Blood as a physicochemical system. XI. Man at rest. J. Biol. Chem., 1937, **118**, 635.
22. Keys, A. B., The carbon-dioxide balance between the maternal and foetal bloods in the goat. J. Physiol., 1934, **80**, 491.
23. Wintrobe, M. M., and Shumacker, H. B., Erythrocyte studies in the mammalian fetus and newborn. Am. J. Anat., 1936, **58**, 313.
24. Andreen-Svedberg, A., On the distribution of sugar between plasma and corpuscles in animal and human blood. Skandinav. Arch. f. Physiol., 1933, **66**, 113.
25. Barcroft, J., Flexner, L. B., and McClurkin, T., The output of the foetal heart in the goat. J. Physiol., 1934, **82**, 498.