Physiology. — *Problems of foetal respiration in the cow.* By J. ROOS and C. ROMIJN. (From the Laboratory for Veterinary Physiology of the State University, Utrecht.) (Communicated by Prof. G. KREDIET).

First Part.

I. *The maternal oxygen- and carbon dioxide dissociation curves during pregnancy.*

In earlier work (1937) it had been established that the influence of pregnancy on the oxygen dissociation curve in the cow differs from that observed by BARCROFT et al. (1934) in the goat in this respect, that in the cow the curve remains within the limits of the field which we had fixed for normal non-pregnant animals, whereas in the goat the curve leaves the normal field at a gestation of 10 weeks, remaining outside during all the further time of pregnancy.

It was in the last two months only that in the cow the lower part of the curve, going until an oxygen pressure of 20 mm maximally, had been shown to become more inflected, so that the right limit of the field was slightly crossed by the curve.

It is true that this field is considerably wider than that in the goat, and also exceeds the dimensions determined for any other animal examined, man included.

The course of the oxygen dissociation curve had been watched in one and the same animal, using 3 cows and starting from the 4th month of pregnancy.

It seemed desirable to us to follow this course of the curves in a greater number of animals and using a different technique, because of the importance of that lower part of the curve for its shape and position, and for its steepness, which had been found to be increased during the last months. The position of the points for low oxygen pressure had not satisfied us and incited to new measurements. At the same time the carbon dioxide dissociation curves (carbon dioxide d.c.s.) had to be determined.

It was our intention to check the limits of the field for the curves of normal non-pregnant animals meanwhile.

Four healthy adult Frisian cows were used for these measurements. The blood was drawn from the jugular vein at various moments of pregnancy as is shown by table 1. (For table 1 see next page).

The blood was collected in a wide glass tube which contained a 5 % solution of ammonium oxalate with $2\frac{1}{2}$ % sodium fluoride. The solution

had been brought to a pH of 7.4. It had a volume of 1/50 of that of the blood with which it was thoroughly mixed. In some experiments the anti-coagulant was used in crystalline form.

TABLE 1.

Number of animal	Duration of pregnancy in months
11	4
	6
	6¼
	8
	9
12	2
	3
	6
	8
	8½
	9
13	6
	7
	7¼
	8½
	9
14	5
	6
	9

However much BARCROFT's differential manometer had satisfied us, VAN SLYKE's constant volume apparatus was used in these experiments because of our interest in the position of the points for low oxygen pressure especially. The advantages offered by this apparatus, when a great number of determinations have to be carried out, was another reason to choose it.

Since a practically unlimited volume of blood was at our disposal, the determinations were made using 2 cc of blood.

The carbon dioxide curves were determined by measuring the carbon dioxide in 1 cc of true plasma, obtained from oxygenated blood, in the usual manner.

Results.

Before describing the oxygen d.c. during pregnancy, the limits for the field within which the curves for normal non-pregnant animals are found will be discussed. The shape, given in an earlier paper (1938), was verified by determining the curves in six normal non-pregnant animals. The new field, demonstrated in Fig. 1, agrees for far the most part with that given previously; its lower part has undergone a slight correction. In the same figure the field for the goat and for man has been drawn for comparison.
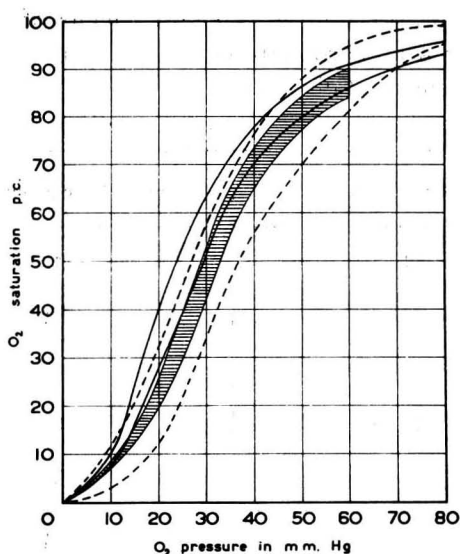
Fig. 1. The area of the O_2 dissociation curves of normal cows, not pregnant, and not having been so recently, is given by the dotted lines. CO_2 pressure 40 mm Hg., temp. 38° C. The field for the goat has been shaded, that for man has been drawn. The curves for the goat and for man according to BARCROFT.

The carbon dioxide d.c.s for true plasma of oxygenated blood, determined at the same time for the same animals, are enclosed by the limits given in Fig. 2. As the reader will find there the reserve alkali varies between 47.5 and 57.5.
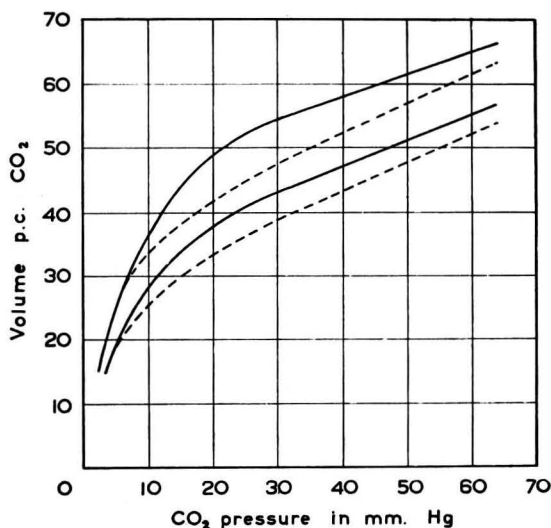

Fig. 2. The area of the CO_2 dissociation curves for true plasma of oxygenated blood of normal cows, not pregnant and not having been so recently, is given by the drawn lines. The dotted field is that for oxygenated blood, as had been determined in previous work. Temp. 38° C.

It is not sure that Fig. 2 gives a fully correct image of the difference between plasma and blood. The state of nutrition of the animals and the kind of nourishment may be supposed to have its influence here, since the true plasma curves were obtained from animals which had passed the summer in the meadow whereas the first set of curves, one excepted, had been determined in the beginning of spring, after the animals had been kept in the stable during the winter. In Fig. 3 a comparison is given of the carbon dioxide d.c.s of whole blood and true plasma from one and the same animal.
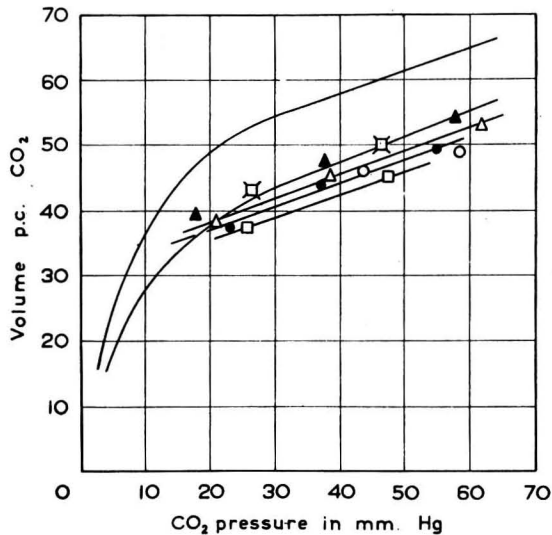

Fig. 3. Carbon dioxide dissociation curves of (a) maternal oxygenated blood (□) and oxygenated true plasma (⋈). The animal was pregnant during 8 months. (b) maternal oxygenated blood (○) and oxygenated true plasma (△) of an animal, pregnant during 7 months, together with those of the foetal blood (● and ▲). Temp. 38° C.

Coming now to the oxygen d.c.s of the pregnant animal, it was established that the influence of gestation is perceivable in two respects. (1) The curves become steeper during pregnancy and (2) they become more inflected during the last 6 months. Speaking in general the position of the curves remains within the limits of the normal field. In some instances the right border line of the latter may be surpassed slightly by the lower end of the curve as a result of the increased inflection observed here during the 7th, 8th and 9th month.

The results, obtained in earlier experiments (1937) with respect to position and shape of the curves have been confirmed. The more steeple position however was found not to be restricted to the last months only, but it was detected to occur earlier, starting from about the 4th month of pregnancy.

In Fig. 4, 5, 6 and 7 a set of oxygen d.c.s is given, together with the carbon dioxide d.c.s, which may be considered as representative.
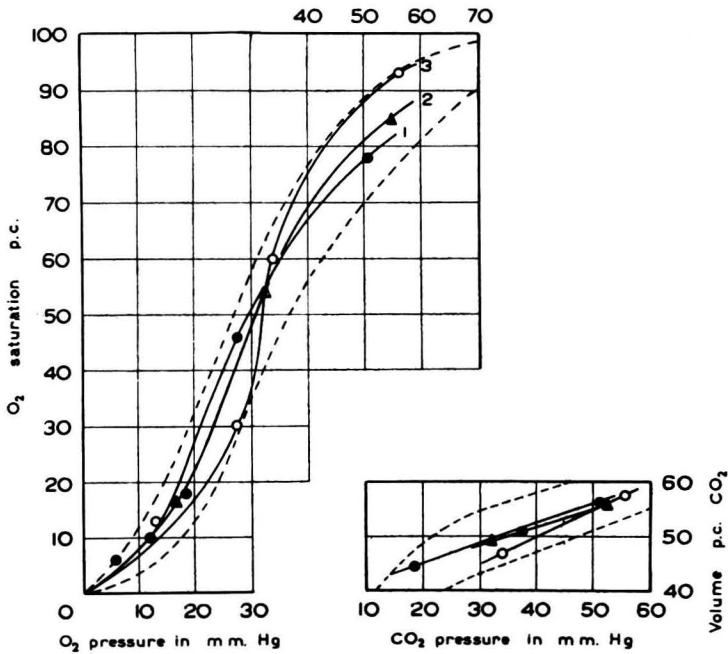
Fig. 4. O_2 dissociation curves and CO_2 dissociation curves of cow 12, pregnant about 2 months (1), 6 months (2) and 8 months (3). The dotted lines give the limits of the field for normal non-pregnant animals. For the O_2 d.c.s. CO_2 pressure 40—43 mm Hg; the CO_2 d.c.s. have been determined for true oxygenated plasma. Temp. for both 38° C.
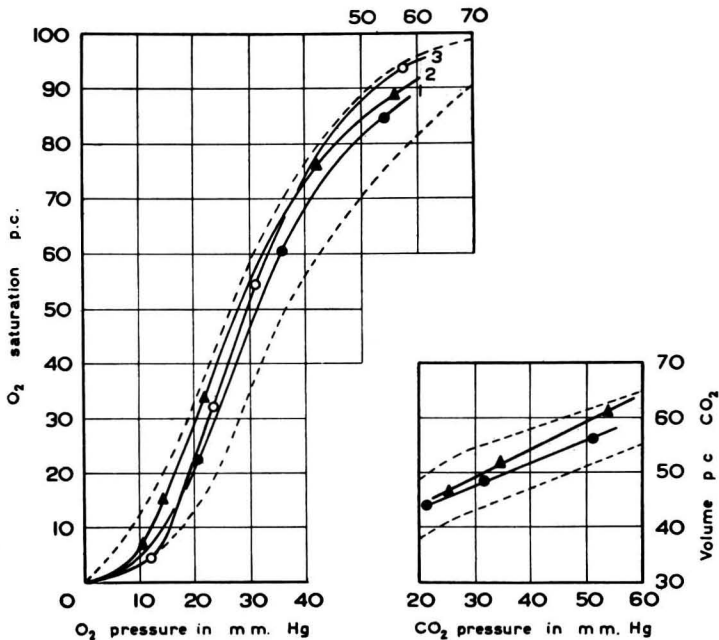

Fig. 5. Cow 13, pregnant 7 months (1) and 9 months (2). The third curve (3) was obtained one week later, 3 hours before parturition. The dotted lines give the limits of the field for normal non-pregnant animals. Rest as in Fig. 4.
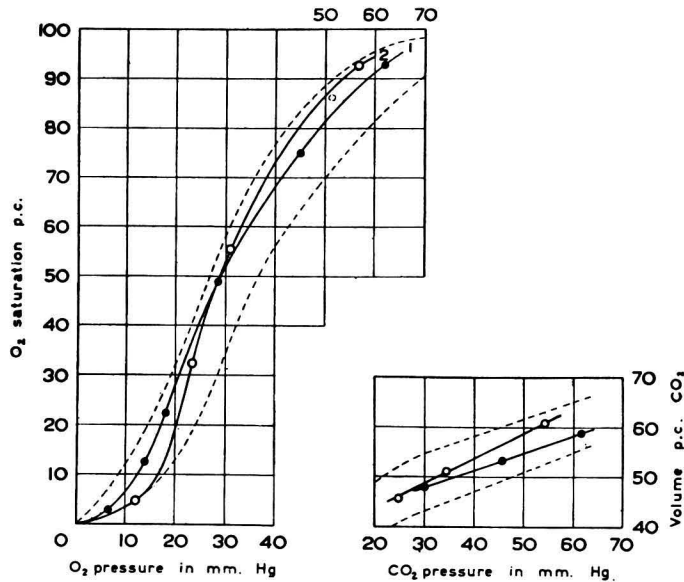
Fig. 6. Cow 13, pregnant 8½ months (1). Curve (2) was obtained from blood, taken 3 hours ante partum. The dotted lines give the limits of the field for normal non-pregnant animals. Rest as in Fig. 4.
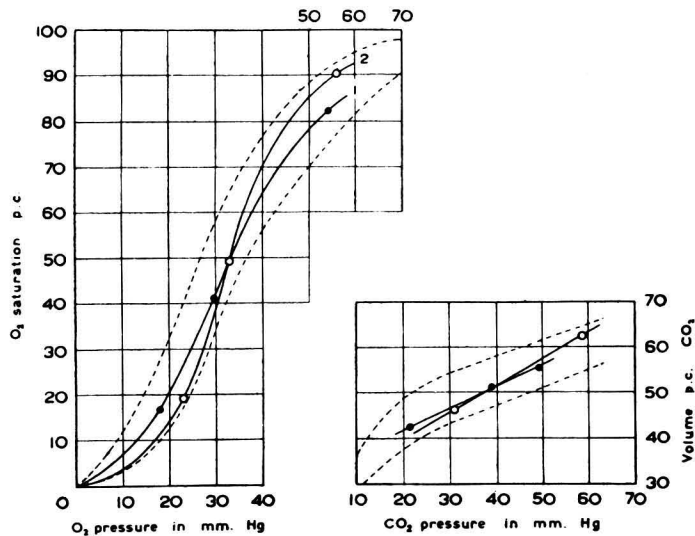
Fig. 7. Cow 14, pregnant 5 months (1) and 6 months (2). The dotted lines give the limits of the field for normal non-pregnant animals. Rest as in Fig. 4.

So it must be concluded that although the changes of the maternal oxygen d.c. during the period of pregnancy may not be called salient, they nevertheless are distinct when the bearing of the curves is watched in one and the same animal.

Concerning the causes by which these changes are produced the only

conclusion that can be drawn with security is this that they are not found in changes of hydrogen-ion concentration.

Firstly it would be difficult to understand how both changes described could be produced by changes of the pH. Moreover the reserve alkali was rather constant during the greater part of the period of gestation, so that its influence was quite insufficient to produce the changes of position of the curves established.

The course of the reserve alkali in the pregnant animal is shown by Fig. 8. It shows that the carbon dioxide combining power of its blood is not lower than in the non-pregnant animal and that there is a noteworthy constancy of alkali reserve up to the ninth month. During that time it ranged between 50 and 55. In one animal (no. 13) it rose somewhat above this limit, reaching 58 in the midst of the 8th month. Then, at the end of the 9th month, a general rise is observed. In two instances in which the blood had been examined immediately before parturition and some few minutes after it, a fall of the reserve alkali could be stated to have taken place during this short time (about 1 hour). The values, found after parturition, have been plotted on the ordinate p.p.
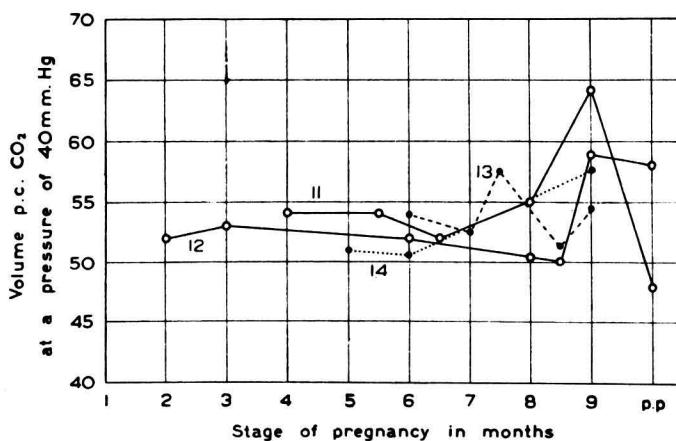

Fig. 8. Reserve alkali during the period of pregnancy in 4 pregnant cows. The figures at the curves give the number of the animals; p.p. = some few minutes post partum. The determinations were made in true plasma of oxygenated blood. Temp. 38° C.

The values of the reserve alkali and those for the hydrogen-ion exponent of true plasma at the various stages of gestation, at a carbon dioxide pressure of 40 mm Hg, are given in table 2. The latter were calculated by using the HENDERSON–HASSELBALCH formula.

In how far the changes of the oxygen d.c.s are due to alterations of the haemoglobin molecule on the one hand and to the effect of electrolytes on the other remains still an open question at this moment.

In none of the animals the maternal alkali reserve was lower than in normal non-pregnant animals. Most often it was found to correspond with the higher part of the normal field for non-pregnant animals.

TABLE 2.

Number of animal	Duration of pregnancy in months	Reserve alkali in true plasma (Vol. p.c. CO_2 bound at a CO_2 pressure of 40 mm Hg)	pH
11	4	54	7.38
	6	54	7.38
	6½	52	7.36
	8	55	7.38
	9	64	7.44
	10 min. p. p.	48	7.33
12	2	52	7.36
	3	53½	7.37
	6	52	7.36
	8	50½	7.35
	8½	50	7.35
	9	59	7.42
	5 min. p. p.	58	7.41
13	6	54	7.38
	7	52½	7.36
	7½	58½	7.41
	8½	51	7.35
	9	54½	7.38
14	5	51	7.35
	6	50½	7.35
	9	58	7.41

It is remarkable that so fundamental differences, as observed here, can be stated to exist at various points between ox- blood on one hand and the blood of man, and even the blood of the goat, on the other, both animals approaching each other so nearly in many respects. In the goat the maternal curve moves in the opposite direction and at the half of gestation it falls outside the normal field where it remains during the further time of pregnancy. BARCROFT et al. (1934) found this displacement to be accounted for by the change in reaction: the increased hydrogen-ion concentration. In the ox there is no displacement to the right side at all and the change of hydrogen-ion concentration is quite different.

Also in man the results obtained in studying the maternal oxygen d.c. differ from those in the ox; EASTMAN, GEILING and DE LAWDER (1933) who examined the curve of the mother immediately after birth of the child, found it distinctly displaced to the right. A corresponding result has been obtained in 1936 by LEIBSON, LIKHNITZKY and SAX.

Consequently the gap between maternal and foetal oxygen d.c. which

is found in the ox- blood as well as in the other species mentioned, is effected in the cow by removal of the foetal curve exclusively.

II. *The dissociation curves of the foetal and the maternal blood.*

Some years ago we examined the relation between foetal and maternal dissociation curve in the cow and published the curves, obtained from an animal, 8 months pregnant (1938). The opportunity to continue the work in a greater number of animals and at various stages of pregnancy was wanting at that moment.

In this chapter the results obtained in a greater number of experiments will be given.

Method.

Both oxygen- and carbon dioxide d.c.s were determined. The maternal blood was taken from a carotid artery, a sample of foetal blood being drawn from one of the umbilical vessels, after Caesarian section had been done under local anaesthesia; the foetus remained connected to its mother under conditions as physiological as possible. The blood was collected in the way as described in the foregoing pages.

The moment of pregnancy at which the curves were determined are clear from the following table.

Age of foetus in months	Sex	Number of cases
3	m	1
$3\frac{1}{2}$	m	1
4	f	1
$5\frac{1}{2}$	f	1
7	f	2
7	m	1
8	f	1
8	m	2
$8\frac{1}{2}$	—	1

Results.

In all cases irrespective of the age of the foetus, the oxygen dissociation curve of the foetal blood was found to the left of the maternal. The difference in position between both was considerable and the foetal curve was found to lie outside the field for normal non-pregnant animals in 9 out

of 11 cases. In the two remaining instances the curves were found either for the greater part or completely within the limits of the normal field.

As was described in the first chapter of this paper the maternal curves remained within the normal field. In some instances the inflection in the last month of pregnancy had increased in such a way that the lower part of the curve crossed the right limit of the field but this was an exception. Of course the curves obtained at various ages of the foetus, can hardly be compared, since they were obtained from different animals.

In the figures 9—13 a set of curves is given for both mother and foetus on various points of foetal life.
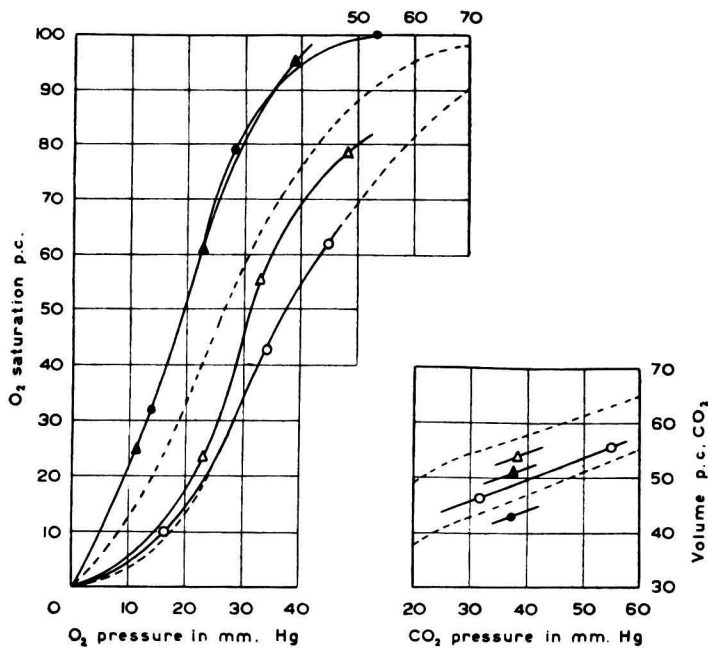

Fig. 9. O_2 dissociation curves of two foetus, old 3 ($\bullet$) and $3\frac{1}{2}$ months ($\blacktriangle$) respectively, together with those of the mothers (($\bigcirc$) and ($\triangle$)). The foetal curves coincide for a great part. CO_2 pressure 42—44 mm Hg., temp. 38° C. At the bottom the corresponding CO_2 dissociation curves for true plasma of oxygenated blood. The field for the normal non-pregnant animals has been dotted.

In all figures given here the foetal curve is found outside the normal adult field, as it was the rule. Two other examples are given by Fig. 14 in which the curve for a foetus, 4 months old, is found to have its position for the greater part within the normal area, whilst the dissociation curve of a foetus of $8\frac{1}{2}$ months is found entirely within that field. If we consider the carbon dioxide d.c.s of Fig. 14 the explanation of these exceptions does not offer difficulties. In both foetus the reserve alkali was low and remained below the normal field. In the foetus of $8\frac{1}{2}$ months it was even extremely low and less than 50 p.c. of the value which may be considered
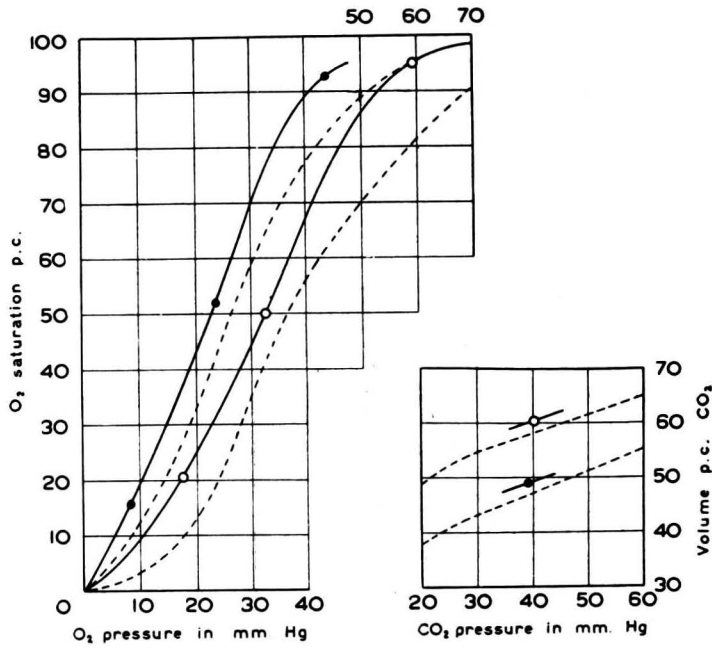
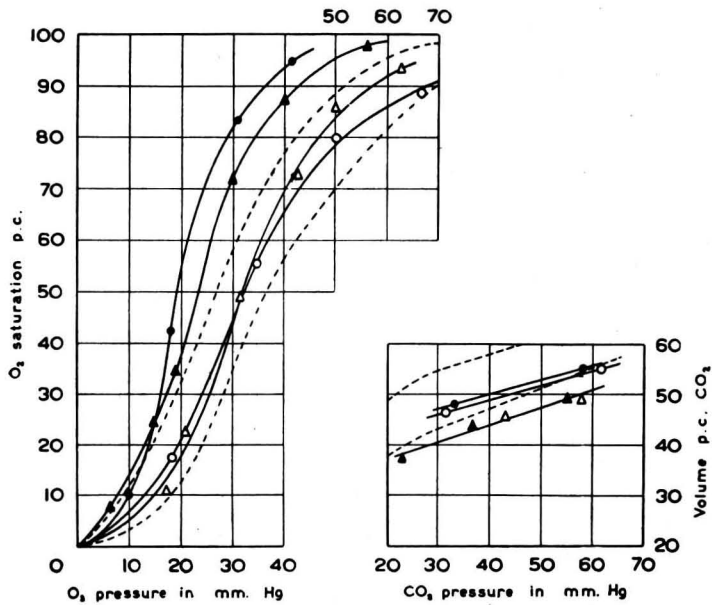Fig. 10. Age of the foetus 5½ months. The rest as in Fig. 9.

Fig. 11. Age of both foetus 7 months. The rest as in Fig. 9.
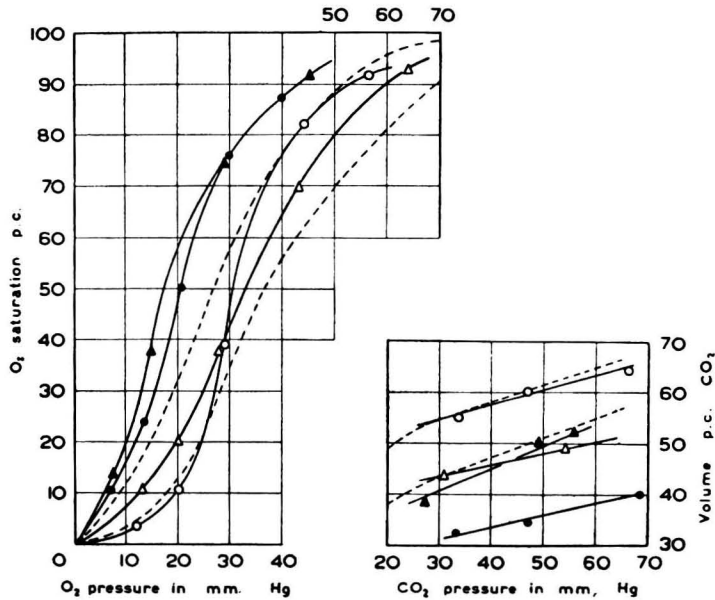
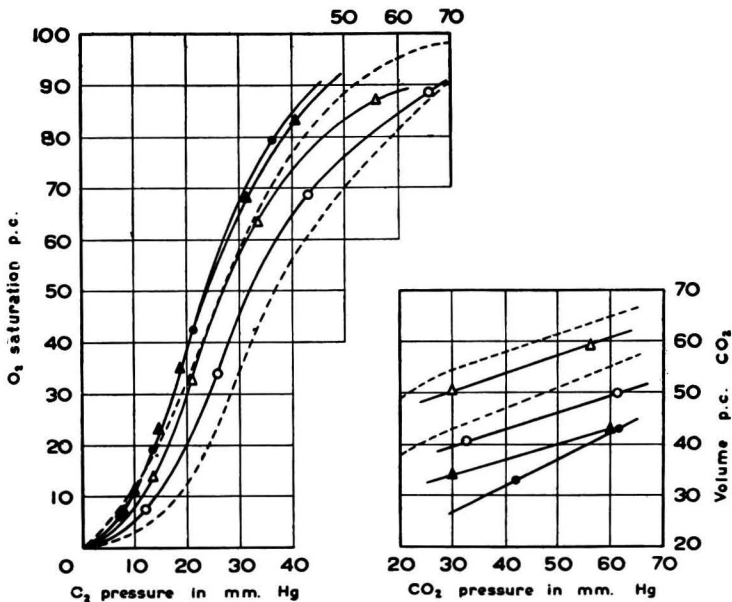Fig. 12. Age of foetus 7 (●) and 8 (▲) months respectively. The rest as in Fig. 9.

Fig. 13. Age of both foetus 8 months. The rest as in Fig. 9.

as being normal. It is the Bohr effect by which the position of the curves of Fig. 14 is brought about.

How is the course of the reserve alkali during foetal development?

During the first 6 months of intra-uterine life the foetal carbon dioxide

curves fall within the field, established for normal non-pregnant animals, be it in its lower part. In the seventh months' foetus the curve was found a little below that field. As intra-uterine life procedes the gap between the two increases (See Fig. 12 and 13). This had also been found in the foetus of 8 months, described in an earlier paper (1938).
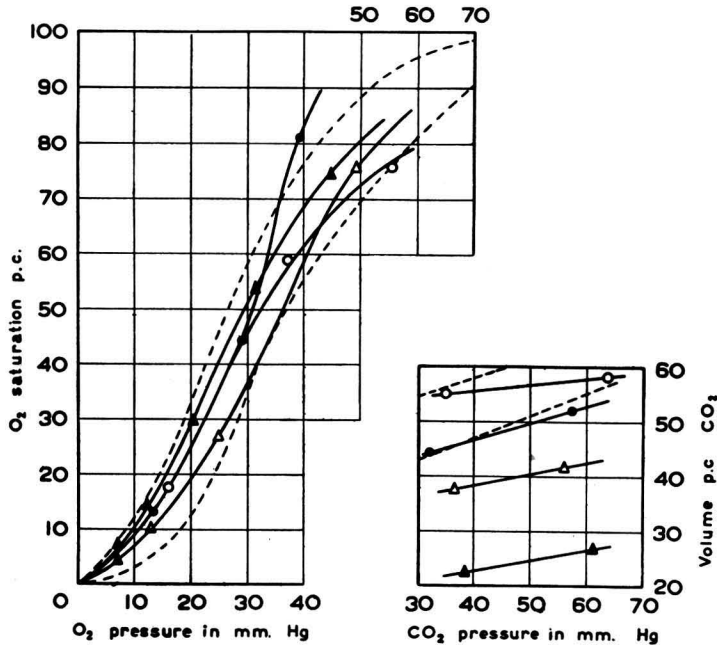

Fig. 14. Age of foetus 4 (●) and 8½ (▲) months respectively. The rest as in Fig. 9.

In the mother cows the reserve alkali was rather high also in this series. Up to about the 7th month of pregnancy the position of the curves correspond even to the higher half part of the normal field for non-pregnant animals. Later on a rather great dispersion of results was observed, which must probably be attributed to the condition of nutrition of the animals of this series. The pregnant animals described in chapter (I) were all fully sound and in an excellent state of nutrition. They belonged to the permanent stock of cattle of one of the Veterinary Institutes of the Faculty. The animals however which were sacrificed to the experiment together with their foetus had been bought for this purpose. Their state of nutrition was considerably less. So the lower reserve alkali, found in some of them will probably find its explanation in this circumstance. In 8 out of 11 experiments maternal reserve alkali was considerably higher than the foetal, in the remaining 3 cases there was scarcely any difference between the two.

A review of the reserve alkali, measured in both mother and foetus, is given in Fig. 15. Besides the 11 animals treated in this chapter, other

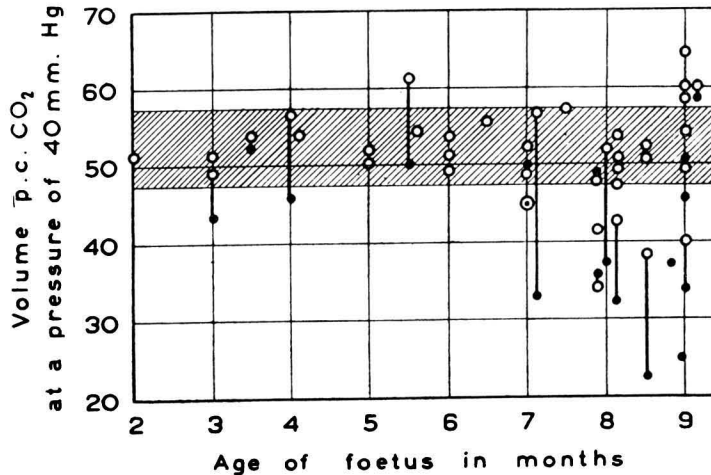measurements made in pregnant and in new-born animals, have been collected.

Fig. 15. Reserve alkali in maternal blood (○) and in blood of the foetus at various ages (●). The CO_2 dissociation field for normal non-pregnant adult animals has been shaded. The points indicate the volume p.c. CO_2, bound by true plasma at a gas pressure of 40 mm Hg.

The figure shows the relation between mother and foetus and moreover the fall of foetal reserve alkali in the last months.

Returning to the oxygen d.c. another point of difference between maternal and foetal curve has still to be stated, viz. concerning the shape of the curve. The foetal curve is less inflected than the maternal and during the first six months of prenatal life especially its lower part is so stretched that the hyperbolic form is approached. Until the 7th month this shape is conspicuous as may be seen in the figures 9, 10 and 14. So the moment of change in the foetal oxygen d.c. obviously coincides with the fall of alkali reserve.

Discussion.

This coincidence may be of importance for the foetus from a physiological point of view since both changes cooperate in facilitating giving off oxygen in the area of low oxygen pressure, as will be found in the foetal tissues. Especially the stretched oxygen d.c. may be called favourable. It is not only the oxygen binding power which, at a low oxygen pressure, is thus promoted but the volume of oxygen given off will be relative great at a slight fall of oxygen pressure. So the respiratory needs of foetal tissues during the first months may be considered as being contented in a very satisfactory way in consequence of this hyperbolic curve.

As the young embryo grows the oxygen needs of its tissues, the muscles especially, will increase considerably and the process of gas change will

be performed at a higher level of the curve, i.e. at a higher oxygen pressure. The more inflected curve, exhibited by the foetal blood starting from the 7th month may be considered to meet this demand in a striking way. In the area of higher oxygen pressure oxygen will be given off now more readily than it was allowed by the hyperbolic curve.

A set of oxygen dissociation curves has been given for the goat by BARCROFT et al. (1934). These authors also found a gap between maternal and foetal curves but it was produced by displacement of both maternal and foetal curve. Whereas the foetal curve was found to the left of the normal, starting from about the 12th week, the maternal was drifting to the right and had already left the normal area at the 10th week of gestation.

The carbon dioxide balance between maternal and foetal blood in the goat was examined by KEYS (1934). His results differ considerably from ours, observed in the ox. Contrary to our findings he found a markedly higher alkali reserve in the foetal than in the respective maternal blood. The average foetal blood was able to bind 22 p.c. more carbon dioxide than the corresponding maternal at the same tension. The foetal reserve alkali was not much lower than what he considered as normal for the goat. The maternal one however was considerably below it. Unfortunately KEYS did not measure the reserve alkali in true plasma of either oxygenated nor reduced blood but in whole blood. If we try to make his figures comparable with ours the result is that the reserve alkali in true plasma of oxygenated blood was here between 35 and 40 in 4 cases and about 45 in the fourth.

It is difficult to follow his conclusions concerning the course of the reserve alkali during foetal life since they are based on determinations, partly made by others and the impression is given that they were made under conditions which were not very favourable.

Some figures for the reserve alkali in the pregnant woman are found in literature. The conclusion is that there is a definite drop of reserve alkali as pregnancy proceeds. WILLIAMSON (1923) found a minimum (33 in multiparas, $43\frac{1}{2}$ in primiparas) at the end of gestation. After parturition it rose so that on the 10th day after delivery a normal level was reached again. In the child at term the carbon dioxide binding power of the blood was considerably higher than in the maternal blood.

So there are points of difference in many respects between the goat and the ox.

1. In the goat the first sign of pregnancy is exhibited by the maternal curve which, according to the authors as the result of increased hydrogen-ion concentration, leaves the normal field between the 7th and 10th week whilst any shift in the foetal curve is still lacking. In the cow there is no fall of reserve alkali in the mother, the maternal oxygen dissociation curve does not move to the right but even slightly to the left, maintaining however its position within the normal field.

2. In the cow the inflection of the curve increases.

3. The foetal curve however is much more mobile in the cow than in

the goat. As soon as in the 3rd month, i.e. in the first third part of intra-uterine life, it has taken its position far from the normal field (Fig. 9), whilst in the goat it is not before the 13th week (i.e. at the end of the second third part of gestation) that its removal becomes distinct and the curve partly falls outside the limits of the normal area.

4. In the goat the higher part of the curve remains inside those limits up to the 19th week.

5. Further the authors mentioned found the foetal and the maternal curves drawing towards one another again in the last week of foetal life of the goat, and one week later, after birth, the foetal curve had returned again in the adult field, both maternal and foetal curve having the normal degree of inflection. In the cow the foetal curve persists considerably longer in its foetal state concerning both position and shape. In the new-born calf the curve, although nearer to the maternal than it was in the foetal time, is still outside the normal field (1937).

So the divergences, exhibited by the foetus, are far more intensive in the cow than in the goat, and apparently the young animal is born in a condition, differing much more from the adult than the kid of the goat does.

6. It is interesting that in the goat the foetal blood, though not more alkaline than the normal, is more alkaline than the maternal. The same is the case in man. The reverse relation is found in the cow.

Although in the cow the difference between maternal and foetal curve is brought about by the properties of the foetal oxygen dissociation curve exclusively, that difference and its importance for foetal respiration is not

TABLE 3.

Oxygen pressure required in order to give an oxygen saturation of 50 p.c.

Age of foetus	Goat (BARCROFT)			Age of foetus	Cow		
	Foetus	Mother	Difference		Foetus	Mother	Difference
10 weeks	32	36	4	3 months	20	37	17
11 „	30	36	6	$3\frac{1}{2}$ „ (3)	18	34	16
$13\frac{1}{2}$ „	24	34	10	4 „	$30\frac{1}{2}$	$32\frac{1}{2}$	2
14 „	30	38	8	$5\frac{1}{2}$ „ (2)	23	33	10
15 „	$24\frac{1}{2}$	37	$12\frac{1}{2}$	6 „	10	30	20
$16\frac{1}{2}$ „	22	35	13	7 „ (3)	20	32	12
18 „	25	40	15	8 „ (4)	20	32	12
$19\frac{1}{2}$ „	21	35	14	$8\frac{1}{2}$ „	29	$36\frac{1}{2}$	$7\frac{1}{2}$
$20\frac{1}{2}$ „	24	34	10				
At birth	30	36	6	At birth (6)	$22\frac{1}{2}$	$31\frac{1}{2}$	9

The figures between brackets give the number of observations from which the average value has been taken.

less considerable. Also in the cow the avidity for oxygen is far greater in the foetal than in the maternal blood, and at a given oxygen pressure foetal blood will be saturated to a notably higher degree than the maternal. This will be evident from the figures, collected in table 3, in which the respective figures observed in the goat by BARCROFT, are given for comparison. The table shows the gas tensions required in order to give a 50 p.c. saturation to the blood. For both mother and foetus, the pressure required is lower in the cow than in the goat at a corresponding moment of pregnancy. The difference however between mother and foetus is generally greater in the cow than in the goat.

In table 4 the figures are given for the reserve alkali of true plasma for both mothers and foetus. The pH has been calculated.

TABLE 4.
Reserve alkali in maternal and foetal true plasma.

Age of foetus in months	Sex	Reserve alkali		Corresponding pH (calculated)	
		mother	foetus	mother	foetus
3	m	49¼	44	7.34	7.28
3½	m	54¼	52	7.39	7.36
4	f	56	46	7.40	7.30
5¼	f	60¼	50	7.43	7.34
7	f	49	49¼	7.33	7.34
7	f	44	44	7.28	7.28
7	m	57¼	33½	7.40	7.15
8	f	43	32	7.28	7.15
8	m	54¼	37¼	7.39	7.20
8	m	47	47	7.30	7.30
8¼	—	39	23	7.22	6.98

In man, in which the oxygen dissociation curve for mother and child was examined immediately after birth of the baby (LEIBSON, LIKHNITZKY and SAX (1936)) the same events have been found as in the goat, in so far that the maternal curve is displaced considerably to the right, whilst the foetal curve corresponds nearly with that of the non-pregnant adult.

This displacement of the maternal curve in man and in the animals, except for the ox, deserves attention because of its physiological consequences. It shows a greater ability of the blood to give off its oxygen and foetal respiration will thus be improved, provided that maternal blood will be oxygenated in the lungs to the same degree in spite of the higher oxygen pressure in the blood. Is it reasonable to assume that in general

alveolar oxygen pressure will be high enough to do so? No doubt it is an interesting point to investigate the composition of alveolar air in the course of pregnancy. It may be remembered here, that during pregnancy we found an increase of oxygen content of the alveolar air in the dog (1937). Starting from the 4th week of pregnancy, i.e. before the midst of foetal life, alveolar oxygen pressure increased with 6 to 12 p.c., whilst at the same time carbon dioxide pressure had fallen to under 90 p.c. of its original value.

In the description of our first observation, two years ago, it was already emphasized that differences of reserve alkali could not be responsible for the difference between maternal and foetal oxygen d.c. The new experiments affirm this conclusion since the pH of the foetal blood either agreed with that of the maternal or even remained below it. In spite of this fact the foetal oxygen curve was found at the left, which feature proves that the displacement to the right, promoted by the altered hydrogen-ion concentration, is counteracted by another influence by which it is inverted to a displacement in the opposite direction. Moreover it is not the position only but also the shape, by which both curves differ.

It is very probable that the signs observed are effected by the properties of foetal haemoglobin, which differ from those of the maternal. For the chemical work done in this field by many workers, the reader may be referred to a report given for the Sixteenth International Physiological Congress (1938). The question in how far electrolytes play a part here, cannot be settled.

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