The Application of the Theory of Heat Exchangers to a Physiological Study of the Goat Placenta

by

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INTRODUCTION

"The first man knew her not perfectly and in like manner the last hath not traced her out." ----Ecclesiasticus (84).

The mammalian placenta is defined as:

> "The vascular organ in mammals except monotremes and marsupials that unites the fetus to the maternal uterus and intermediates the metabolic exchanges of the developing individual through a more or less intimate association of chorionic and usually allantoic and of uterine mucosal tissues by which the fetal and maternal vascular systems are brought into intimate relation permitting exchange of materials by diffusion but without direct contact between fetal and maternal blood and which typically involves the interlocking of fingerlike or frondose vascular chorionic villi with corresponding modified areas of uterine mucosa" (32).

This rather cumbersome definition describes the placenta as an exchanger but it should be realized that the mammalian placenta has other functions. Guyton (34) describes the placenta as an exchanger which also functions as a nutrient storehouse for the fetus and as an endocrine gland for the production of various hormones. The two latter roles do not concern this discussion and subsequent references to the mammalian placenta will be concerned only with the description of this organ as an exchanger.

For many years the placenta has been known to function as an exchanger. In 1564, Arantius (4) observed that the fetal and maternal circulations were separate within the uterus. Ray in 1701 wrote the following:

> "Against what we have said of the necessity of the Air for the maintenance of the Vital Flame, it may be objected, That the Foetus in the Womb lives, its Heart pulses and its Blood circulates; and yet it draws no Air, neither hath the Air any access to it. To which I answer, That it doth receive Air, so much as is sufficient for it in its present state, from the maternal Blood by the Placenta.... I say then, That the chief Use of the Circulation of the Blood Thro' the Cotyledones of a Calf in the Womb (which I have often dissected) and by Analogy thro' the Placenta.... in an Human Foetus, seems to be the Impregnation of the Blood with Air, for the feeding of the Vital Flame" (73).

The succeeding years have not produced much in the way of clearly defined facts that can be added to this statement. The main body of the literature pertaining to placental exchange is based on descriptive studies. The rationale behind this approach is that the description of the physical characteristics of the placenta should permit predictions to be made concerning its behavior over a range of conditions. To this end, many anatomical and histological studies of the placenta have been made. The volumes and flows in the

uterine and umbilical vasculature have been measured and the resistance to diffusion imposed by the exchanging surfaces has been approximated by observing the transfer of respiratory gases.

The development of these various studies and their usefulness in the light of more recent approaches will be discussed in this introduction. It will be shown that the placenta is a complex organ and that a clear understanding of its function is unlikely to be gained from a description of its physical characteristics. The recent awareness of this limitation has resulted in several original and diversified approaches to the study of the mammalian placenta in which modern techniques are directed toward an examination of what the placenta does rather that what it is. The development of functional analyses will be discussed and the special usefulness of analyses based on the theory of heat exchangers will be demonstrated. The succeeding chapters will describe in full detail an experiment in which the theory of heat exchangers was applied to a study of transplacental diffusion in the goat placenta. The aim of the experiment was to observe the transplacental diffusion of inert gases in the goat over a wide range of conditions. The results of this experiment allow conclusions to be drawn as to the vascular architecture of the uterine and umbilical circulations in the goat placenta.

VASCULAR ANATOMY

The most crucial question that must be answered, if the placenta is to be described, concerns the arrangement of the exchanging capillaries. There are three simple models to which the cotyledonary placenta has been compared.

1. Concurrent Flow Pattern

In this model the maternal and fetal capillaries are in the same plane and run parallel to one another. The flow of blood is in the same direction in each capillary. This means that the maternal and fetal arterial ends of the capillaries are adjacent to one another as are the maternal and fetal venous ends of the capillaries.

2. Countercurrent Flow Pattern

This model is similar to the concurrent model except for the fact that one of the flows is reversed. This means that the maternal arterial and fetal venous ends of the capillary are adjacent to one another as are the maternal venous and fetal arterial ends of the capillaries.

3. Crosscurrent Flow Pattern

In this model the maternal and fetal capillaries cross at right angles to each other. The exchanging characteristics of this system are more difficult to define than those for the concurrent and countercurrent models.

Several attempts have been made to classify the cotyledonary placenta as one or the other of these models. Earlier workers have favored the simpler configurations but more recent observations indicate that this type of placenta may be quite complex. Ease of computation demands that the simplest useful model be adopted. This section is in the form of an evaluation of the evidence presented for, and against, the representation of the sheep placenta as a simple countercurrent exchanger.

A detailed anatomical description of the goat placenta is not available but there is a wealth of information pertaining to the sheep placenta. In the absence of evidence to the contrary, it will be assumed that the fundamental anatomical characteristics of the goat placenta are the same as those of the sheep. In support of this assumption is the fact that both the domestic goat (Capra hircus) and the domestic sheep (Ovis aries) are closely related members of the family Bovidae (81). Further evidence is given in Table 1 taken from Hafez's comparisons of some relevant characteristics of these two species (35). Physiological evidence was provided by Meschia et al. (57) who examined the transplacental diffusion of antipyrene in sheep and goats. The results of these experiments did not demonstrate any differences between these two species.

TABLE 1

Breeding, gestation and prenatal development in the sheep and the goat (35).

Species	Birth weight Kg.	Puberty weight Kg.	Adult weight Kg.	Gestation period days	Type of Placentation		Litter size
					Gross shape	Relation to endometrium	
Goat (*Capra hircus*)	3-4	25-30	50-80	146-151	cotyledonary	transitional* syndesmochorial**	1-3
Sheep (*Ovis aries*)	3-4.5	25-42	70-80	144-152	cotyledonary	transitional* syndesmochorial**	1-3

* Huxley classification

** Grosser classification

The following brief description of the gross anatomy of the cotyledonary placenta taken from Wimsatt (83, 84) should assist in the understanding of subsequent detailed descriptions of vascular anatomy. A fundamental characteristic of the placentas of higher mammals is the formation of vascular chorionic villi which either penetrate directly into the endometrium or simply interdigitate with vascular outfoldings of the endometrial surface. Their function is to bring the fetal (allantoic) vessels into proximity of the maternal vessels. In sheep, as in all ruminants, the villi arise in separate tufts called cotyledons which are widely scattered over the chorion forming a cotyledonary or multiplex placenta. The cotyledons are separated by extensive areas of chorion, lacking villi, the intercotyledonary or membranous chorion. The membranous chorion faces a uterine surface which is relatively smooth and the cotyledons protrude into local rounded elevations of the endometrium called uterine carunculae. The carunculae, plus the villi entering their crypts, constitute the placentomes. The sheep placenta has between 60 and 100 placentomes which increase in size and number to about the 80th day of gestation, after which they become smaller and sometimes less numerous.

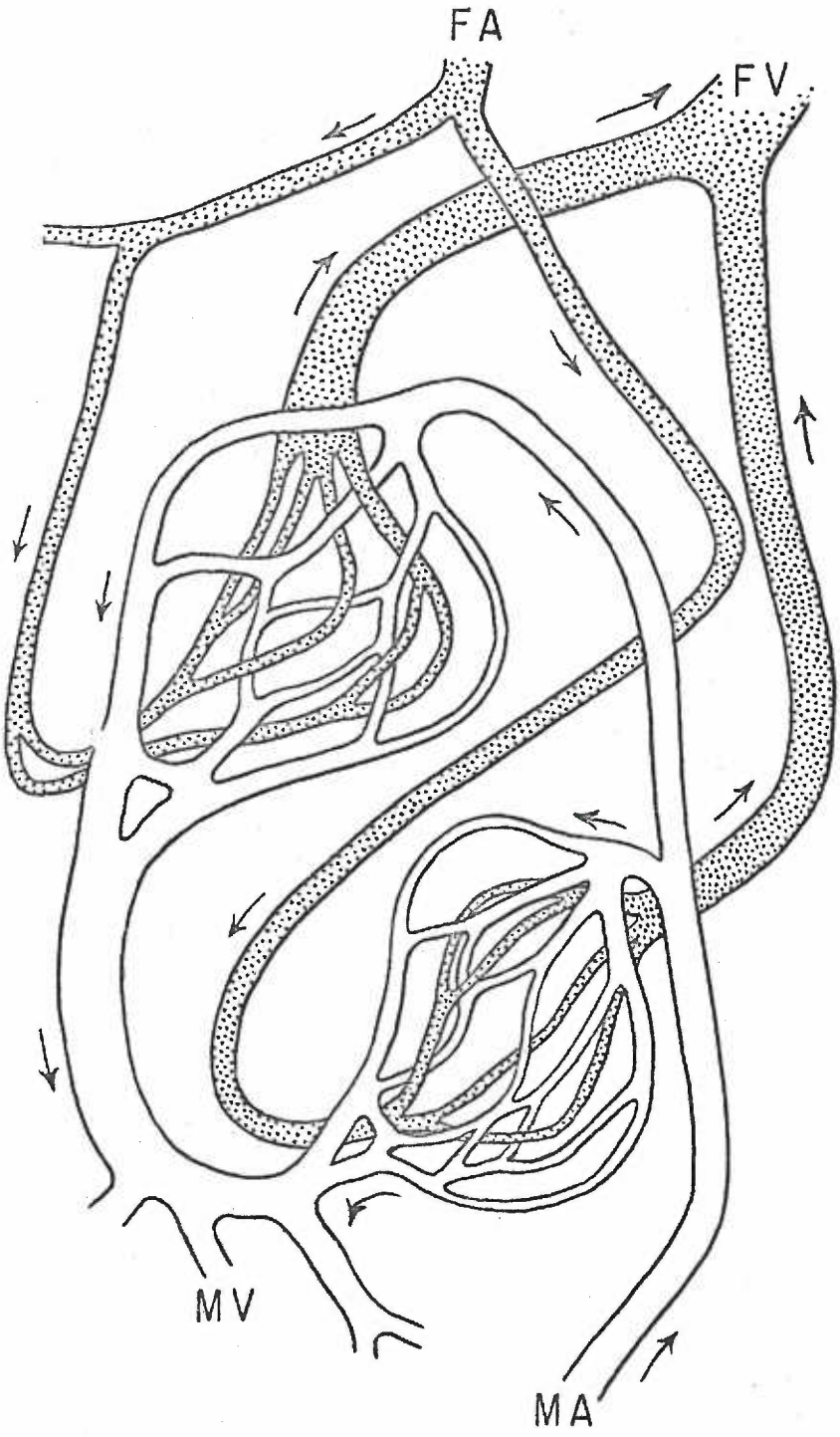
Wimsatt (84) claims that the sheep placenta should be classified as syndesmochorial because only the surface epithelium is eroded, resulting in apposition between endometrial connective tissue

and chorion. This may not be strictly correct; in a recent review Metcalfe, Bartels and Moll (58) pointed out that electron microscopic studies show a thin epithelial sheet and that the classification of the sheep placenta should be changed to epitheliochorial.

The first detailed study of the vascular anatomy of the sheep placenta was done by Barcroft and Barron (8) in 1946. The results of this much quoted work have been seriously questioned in recent years. Before discussing the work itself it will be valuable to examine the climate of opinion at the time it was done.

In 1887 Tafani (80) described the placenta of the cat and showed that the maternal and fetal capillaries were arranged in a countercurrent configuration. The maternal blood flows from the fetal surface of the placenta towards the uterus and the fetal blood flows from the uterine side towards the fetal side. Tafani made no comment about the physiological significance of the finding. In 1926 Mossman (63) observed the same phenomenon in the rabbit placenta (see Figure 1). Realizing the importance of this configuration, Mossman pointed out that in a countercurrent placenta the umbilical vein would contain more oxygen and less carbon dioxide than if the vessels were in a concurrent configuration. Mossman clearly understood that a countercurrent placenta was more advantageous to the fetus than a concurrent placenta and that the rabbit placenta was of this advantageous type. He further stated that, "The adaptation seems to me to be of such

Fig. 1. Diagram of the maternal and fetal circulation of the twenty-two day placenta of the rabbit. Redrawn from Mossman (63). Clear areas are the maternal vessels, dotted areas are the fetal vessels.

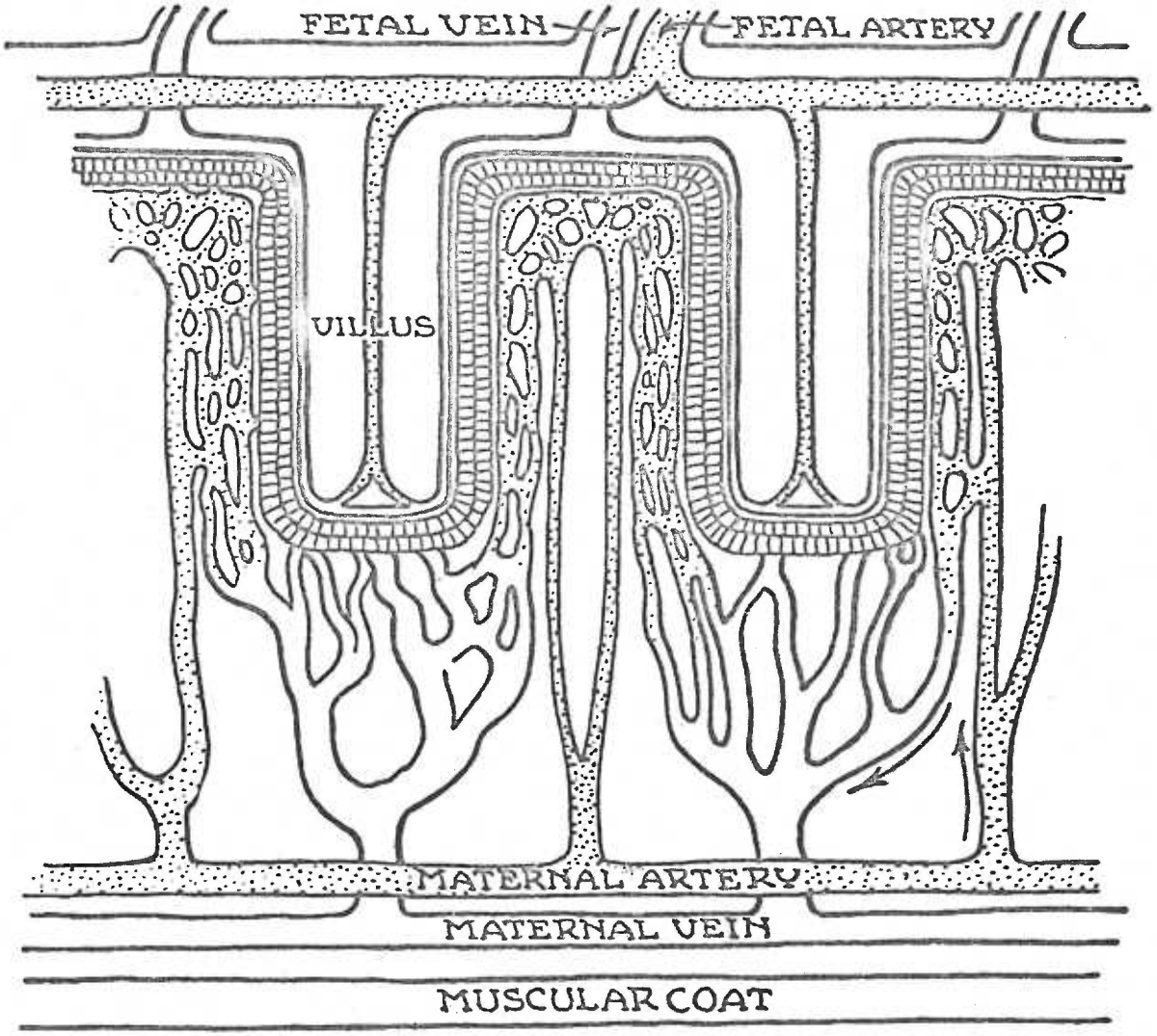

FA
FV
MV
MA

fundamental importance in a labyrinthine placenta that I expect to find it in all of them" (63). Barcroft and Barron (8) did their anatomical studies with a full awareness of Mossman's work and may have anticipated that the sheep placenta would be of a counter-current type.

Barcroft and Barron (8) examined the placentas of 15 sheep at various stages of gestation. The maternal and fetal sides of the uterus of 7 sheep were injected with gelatin. In the remaining 8 sheep, colored latex was used instead of gelatin. The pattern of the distribution of the maternal and fetal vessels within the cotyledons was first determined from graphic reconstruction of the vessels made from serial sections of individual cotyledons. Where latex injection was used, the tissue was digested in KOH solutions and individual blood vessels traced from the artery through the capillary bed and into the collecting veins. These observations are of great historical importance and are illustrated in Figure 2.

Figure 2 shows how the maternal uterine arteries, after considerable branching, run from the uterine surface towards the placental surface at which point they break into a dense capillary network which extends to the placental surface of the cotyledon. These capillaries lead back into the cotyledon running roughly parallel to the artery. They join to form a loose network in which the longitudinal members predominate. Near the base of the cotyledon

Fig. 2. Diagram illustrating the arrangement and the relations of the fetal and maternal vessels within the cotyledonary portion of the sheep's placenta. Reproduced from Barcroft and Barron (8).


FETAL VEIN
FETAL ARTERY
VILLUS
MATERNAL ARTERY
MATERNAL VEIN
MUSCULAR COAT

on the uterine side the capillaries unite to form small veins.

On the fetal side small branches of the umbilical artery pass over the cotyledonary surface and descend into its central cavity. The arteries then branch repeatedly and penetrate the walls of the cotyledon. Each villus has one of these branches running centrally through the core. This central artery does not usually branch until it reaches the tip of the villus where it divides into three or four branches which give rise to a capillary plexus which covers the entire surface of the core. There are no venules within the core of the villus. Barcroft and Barron (8) summarize these findings in the following statement: "...the blood flows in opposite directions in parallel nets of maternal and fetal capillaries".

This observation has not been confirmed by more recent studies. Wimsatt (83) took issue with several of the observations of Barcroft and Barron. He clearly showed that there are veins within the core of the villus which drain the fetal capillary network and that the fetal capillary flow need not necessarily be from the apex to the base of the villus. In 1964 Steven (77) described fetal veins extending into the branches of the villus almost as far as the arteries. Steven concluded that local flow from artery to vein may occur at all levels of the villus. Further support is provided by Harrison and Hamilton (37) who reported observing this type of flow in the placenta of Père David's deer.

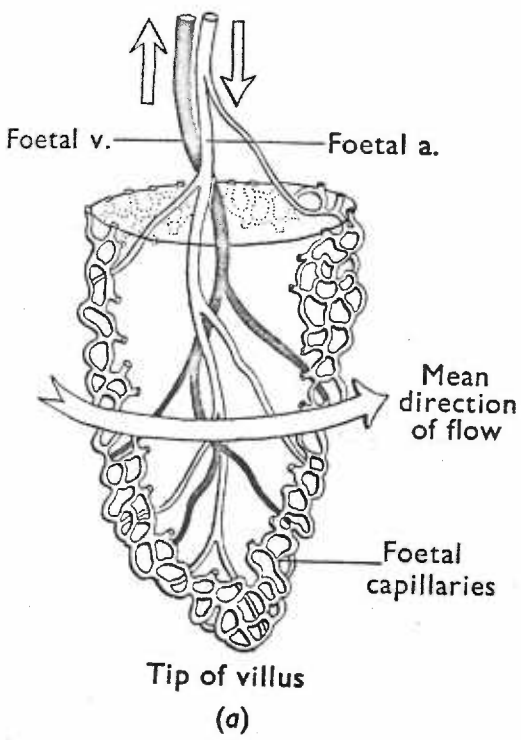
Metcalfe et al. (59) reasoned that if the sheep placenta was countercurrent as described by Barcroft and Barron then the amount of nitrous oxide (N_2O) transferred from the fetal to the maternal side during retrograde perfusion of the placenta should be different from and less than that transferred during normal perfusion. They found that reversing the flow direction in the fetal umbilical vessels resulted in a slight increase in the N_2O concentration in the effluent perfusion fluid. From these observations Metcalfe et al. concluded that no functionally effective countercurrent flow pattern exists in the sheep placenta. This result should be accepted as corroborative but not conclusive because the effect of retrograde perfusion on the physical systems determining N_2O exchange in the placenta remains undefined.

In a further study of the sheep placenta, Steven (78) injected fetal and maternal placental vessels with dilute neoprene latex for micro-dissection and corrosion studies or with India ink for histological staining. These observations are shown in Figure 3. Steven concluded that: "the disposition of the maternal capillaries and the arteries and veins with which they connect supports the view of Barcroft and Barron that maternal blood flow at the capillary level is directed from the center to the periphery of the placentome and therefore parallel with the long axes of the fetal villi. On the fetal side it appears probable that capillary blood may flow locally from

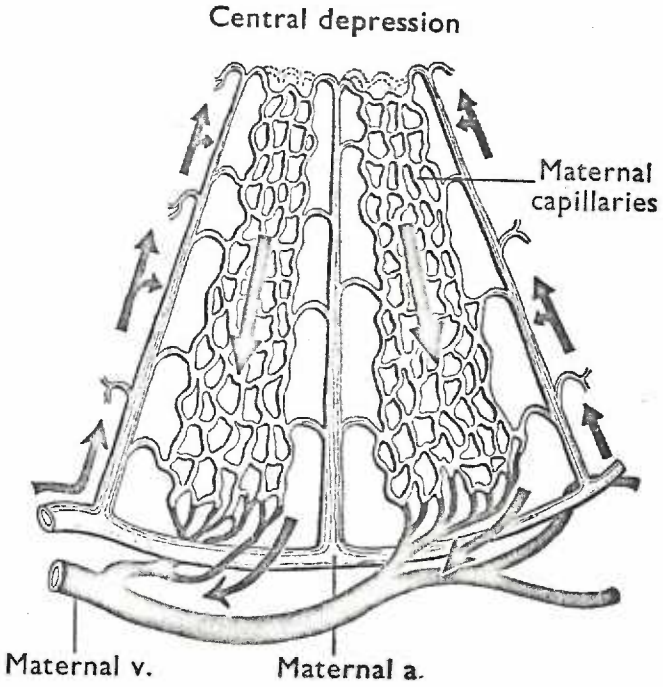
Fig. 3. (a) Diagram to show the arrangement of fetal vessels at the tip of a villous branch.

(b) Diagram to show the arrangement of maternal vessels surrounding the fetal villi.

Reproduced from Steven (78).


Foetal v.
Foetal a.
Mean direction of flow
Foetal capillaries
Tip of villus

(a)


Central depression
Maternal capillaries
Maternal v.
Maternal a.

(b)

artery to vein in any direction but that the mean direction of flow is at right angles to the long axis of the villus. On this hypothesis the system illustrated in figure 3 may be considered as intermediate between a state of concurrent and countercurrent flow" (78).

This conclusion is compatible with the results of Metcalfe et al. (59) and with the observations of Wimsatt (83) but not with the work of Barcroft and Barron (8). The countercurrent configuration postulated by Barcroft and Barron is much easier to work with than the other models suggested and is still assumed for the purposes of calculation by many workers in the field. In the light of the preceding discussion it is possible that large errors may be introduced into any calculation based on the assumption that the exchanging vessels of the sheep placenta are in a countercurrent configuration.

PLACENTAL HEMODYNAMICS

The attempts to describe the vascular architecture of the sheep placenta were described in the preceding section. The next subject to be considered concerns the vessels themselves. Three types of observations have been made in this regard: the volume of blood in the vessels, the flows and the pressures required to generate these flows. The measurement of each of these quantities requires the application of separate techniques. These techniques will be discussed and the results obtained will be evaluated. It should be

pointed out that the acquisition of a set of values is one thing but the extrapolation of these values from the conditions under which they were acquired to the awake, unanesthetized animal must also be justified. This justification has not always been adequate. The major issue in the field of placental hemodynamics is not how to measure the parameter but how to relate the measurement to other values obtained under different circumstances.

A. Volume

It is not difficult to measure the volume of blood in an organ and it is surprising that there are so few measurements of this quantity in the utero-placental circulations. The most useful value to know would be the volume of blood in the exchanging capillaries, a measurement that is quite difficult to make. This information when combined with flow measurements would lead the way to an evaluation of the surface area available for exchange. The literature is evaluated in terms of its usefulness in estimating this quantity.

The volume of blood in the uterus has not been determined in the sheep or goat and the measurement of this quantity has not excited much interest to date. As the understanding of transplacental diffusion develops in the next few years it is probable that measurements of uterine blood volume will be made, especially that fraction

of the uterine blood volume that is contained in the capillaries.

The placental blood volume has been determined by several workers. The interest stems from the fact that placental blood volume is a considerable fraction of the fetal blood volume and therefore relatively more important to the fetus than the uterine blood volume is to the mother. Barcroft (6) describes the work of Cohnstein and Zuntz who measured the ratio of the distribution of blood between the placenta and the fetal rabbit in 1884. The first measurements of fetal blood volume were made by Elliot Hall and Huggett in 1934 (26). Interestingly enough, Elliot et al. used goats in this experiment and found that the fetal and placental blood volume near term was approximately 400 ml. The measurements were made by dye dilution using chlorazol-sky-blue dye. No attempt was made to separate the placental blood volume from the fetal plus placental blood volume.

Barcroft was dissatisfied with the technique employed by Huggett's group and in 1938 became acquainted with the work of Kennedy and Millikan (46) who developed a coloremetric determination of Evans Blue dye (T1824) using a photoelectric cell. Barcroft and Kennedy (10) used Evans Blue to measure the blood volume of the fetus and that of the placenta in sheep. They found that the blood volume of the placenta of fetal lambs was approximately 100 ml. at the 80th day of gestation and did not change as gestation advanced

even though the volume of blood in the whole fetal circulation increased from about 150 ml. at the 80th day to approximately 600 ml. at term. The proportion of the total fetal blood contained in the placenta therefore fell from 53% to 15% during this period. Prystowsky et al. (72) reported that the plasma volume of the near term sheep fetus and placenta at altitude, as determined with Evans Blue dye, was the same as that given by Barcroft and Kennedy. The fetal and placental blood volume was slightly greater at altitude due to an increased hematocrit.

Recently Novy and Metcalfe (66) calculated the volume of blood in the near term goat placenta from measurements of umbilical blood flow and mean transit times. They used indocyanin green dye and the theoretical principles described by Zierler (85). They found that the mean circulation time in the umbilical circuit was 7.2 seconds, and that the placental blood volume averaged 39.2 ml/kg of fetus. The application of this figure to Huggett's near term goat fetus number 22 which weighed 2.9 kg gives an estimate of placental blood volume of 113 mls. This agrees well with 100 mls. in the near term sheep placenta reported by Barcroft and Kennedy (10). The description of Novy and Metcalfe's work is only available as an abstract at this time and a more detailed evaluation cannot be given until a more comprehensive report is published.

There are two unresolved problems related to these

measurements. Firstly, it is difficult to determine whether the volume of blood in the umbilical cord itself is included in these estimates. In the absence of evidence to the contrary it must be concluded that it is. Secondly, it should be noted that future estimates of placental blood volume using indicator dilution techniques should supply evidence that the indicator does not leave the vascular tree. Meschia et al. (55) found a placental extravascular compartment that equilibrated very rapidly with capillary plasma urea, even though urea did not cross the placenta very readily. It is possible that this extravascular compartment, postulated to be Wharton's jelly, could accept indicators which are confined to the capillaries in other organs.

The blood volume of the uterus has not been determined in the sheep or the goat even though several techniques are available whereby this measurement could be made. The established values of placental blood volume have not been broken down into separate arterial, capillary and venous components so that these values can not be used to predict the area of the exchanging surfaces. In summary, the blood volume of the near term goat placenta, including cord blood volume, appears to be of the order of 40 ml. / kg. of fetus.

B. Pressure

It is not difficult to measure the mean pressure in a blood

vessel provided a catheter can be placed in the lumen of the vessel. The problems of evaluating the literature are that the measurement of systolic and diastolic pressures requires that the recorded pressure must be related to the pressure in the vessel. This can be accomplished by first measuring the frequency response of the recording system. A secondary problem, not unique to the measurement of pressure, is that the observed values cannot necessarily be said to be representative of those in the unanesthetized animal. Pressures have been measured on both the maternal and fetal sides of the placenta but the aforementioned problems have not generally been faced. The following discussion contains an evaluation of the validity of the established values in the literature.

The blood pressure in the uterine and ovarian arteries is essentially the systemic arterial blood pressure of the mother. Metcalfe and Parer (60) report that the systolic arterial blood pressure of the unanesthetized sheep in the last 30 days of pregnancy was 87 mm. Hg and that the diastolic pressure was 77 mm. Hg. The mean systemic arterial blood pressure was not reported nor was there a description of the frequency response characteristics of their measuring system. Some loss of gain may be expected so that the actual systolic arterial pressure would be greater than 87 mm. and the actual diastolic pressure less than 76 mm. Meschia et al. (57) reported the mean pressure difference across the uterine circuit in

the anesthetized near term sheep to be between 90 and 100 mm. Hg. These data were obtained by measuring the mean maternal carotid arterial pressure with a transducer and assuming that uterine venous pressure was close to zero. These are higher values than those obtained by Metcalfe and Parer and a reasonable conclusion would be that the mean pressure difference across the uterine circuit in the near term sheep is between 80 and 100 mm. Hg.

Pressures on the fetal side are more adequately defined. Barcroft (8) described the findings of Cohnstein and Zuntz who reported the umbilical arterial pressure in near term lambs to be 83 mm. Hg and the pressure in the umbilical vein to be 27 mm. Hg. Barcroft believed that both of these pressures were excessively high. In a carefully conducted series of experiments Barcroft and Barron (7) measured the umbilical arterial and venous pressures in the near term pregnant sheep under spinal anesthesia. The pressure was determined from measurements of the height of the saline meniscus in a vertical tube attached to a needle in the appropriate vessel. The data obtained were very variable with the mean umbilical arterial pressure in the near term fetus ranging from 40 mm. Hg to 70 mm. Hg. The mean umbilical venous pressure ranged from 9 mm. Hg to 18 mm. Hg and Barcroft and Barron state that excessively high umbilical venous pressures may be due to vascular spasm induced by manipulation of the cord. Dawes (24) reported the mean umbilical

venous pressure in near term lambs to be 10.5 (range 8-14) mm. Hg and the fetal aortic pressure to be 65 mm. Hg with a 10 mm. Hg drop along the umbilical artery. The umbilical arterial pressure midway down the cord would therefore be 50 mm. Hg. In a later study Dawes and Mott (25) observed that constriction of the umbilical veins in the near term lamb caused an immediate rise in umbilical venous pressure on the placental side of the constriction and a fall in femoral arterial pressure, proving that manipulation of the cord can give erroneous pressure recordings. Meschia et al. (57) measured the pressure difference across the umbilical circulation of a near term fetus by holding saline filled umbilical venous and fetal arterial catheters in a vertical plane and measuring the distance between the menisci. They found this to be between 25 and 30 mm. Hg in one fetus. This group used goats and sheep indiscriminantly and apparently observed no differences between them because the species of the animal being reported is often not defined. In 1967, Kirshbaum et al. (48) reported that the mean umbilical arterial pressure in 19 near term lambs was 54 mm. Hg, and this measurement did not change when the ewe breathed 100% oxygen.

Parker and Purves have published the best available data on umbilical pressures (68). Their techniques are clearly described and the measurements are carefully made. They used 22 fetuses

from cross bred ewes. The mother was given a spinal anesthetic of 6-10 ml. of 2% xylocaine intrathecally at the lumbo-sacral junction. The abdomen was opened with a high flank incision, the pregnant horn exteriorized and the fetus delivered onto a heating pad. Fetal temperature was maintained at 39·5 - 40° C and respiration prevented. The fetus was anesthetized with 3-6 mg./kg. sodium pentabarbitol and given 1500 IU sodium heparin. Cotyledonary branches of an umbilical artery and vein were cannulated, the catheters being advanced until the tips were in the cord. The cross section of these catheters was less than 1/8 of the lumen of the vessels. Pressure measurements were made with Statham P23 AC strain gauges using the mid-thoracic point of the fetus as a zero reference. The catheters were 30-55 cm. long and the authors report the frequency response to be no better than 10-15 cps. For this reason, Parker and Purves measured the mean umbilical arterial and umbilical venous pressures. They used 14 fetuses ranging in age from 110 to 147 days. The mean umbilical venous pressure of these fetuses was 11.7 mm. Hg (range 9-16 mm. Hg) and did not change with the age of the fetus. The umbilical arterial pressure in these fetuses changed from 37 mm. Hg at 110 days of age to 56 mm. Hg at 147 days of age. There was therefore a steady increase in the umbilical arterial-venous pressure difference from 25 mm. Hg at 110 days to 44 mm. Hg at 147 days of gestation. The

administration of 100% oxygen to the mother did not result in any systematic change in these values but the reduction of the maternal arterial P_{O_2} to 45 mm. resulted in a 2 mm. Hg rise in the umbilical venous pressure and a 16 mm. Hg rise in the umbilical arterial pressure.

In summary, the mean umbilical arterial pressure in the near term sheep and goat is reported, by each of several workers, to be about 55 mm. Hg. This value seems to be stable except during maternal hypoxia. Pulse widths have not been accurately measured in the umbilical artery. Measurements of the pressure in the umbilical veins are more variable and it seems clear that these values will be excessively high unless manipulation of the cord is minimized. Best measurements of the normal umbilical venous pressure place this value close to 10 mm. Hg in the near term sheep and goat. The data pertaining to the pressures in the uterine circulation are sparse and inconclusive. Such data as there are indicate that the uterine arterial pressure is about 90 mm. Hg in the unanesthetized sheep.

C. Blood Flow to the Uterus and Placenta

The measurement of the uterine and placental blood flows has attracted a lot of attention in the field of placental physiology. Many reports attempt to assign a fixed value to these parameters.

This practice has caused considerable disagreement between the results of different groups which would be resolved if it could be shown that the blood flow to the uterus or placenta were a variable quantity which may change from one set of circumstances to another. The techniques and results pertaining to the measurement of these quantities is described in the following discussion.

The earliest attempt to measure uterine blood flow was made by Barcroft, Herkel and Hill (9) in 1933. They collected the uterine venous outflow of the rabbit over known periods of time. This very primitive technique was not improved until Kety and Schmidt (47) showed that an estimate of tissue blood flow could be obtained in a system with varying venous blood concentrations of a diffusible inert foreign gas such as nitrous oxide.

The nitrous oxide method was first applied to the study of uterine blood flow by Assali et al. (5) in 1953 and in 1959 Metcalfe et al. (61) used this method to measure uterine blood flow in near term goats and sheep. Metcalfe et al. used a variety of general anesthetics and catheterized a uterine vein and a femoral artery. Samples were drawn after the abdomen had been closed and the animal was made to inspire a 15% N_2O gas mixture. The uterine venous N_2O concentration took 30-40 mins. to approach the femoral arterial N_2O concentration. They report the near term uterine blood flow in these animals to be 283 ml. per kilogram of fetus per minute

(sd 89.5). The amount of nitrous oxide in the uterus and contents was determined by placing the fetus or fetuses and the uterine-placental tissue in a glass jar which was then filled with a measured volume of saline. After storage for 24 hours the jar was shaken and the N_2O content of the saline determined with the Van Slyke manometric apparatus. Huckabee (40) considers that this procedure is difficult to validate and that the anesthesia and acute surgery would affect the results.

Huckabee et al. (41) used a similar method for the measurement of uterine blood flow in goats using 4 amino antipyrine (4AA) instead of N_2O. They pointed out that 4 AA equilibrates across the uterus in a significantly shorter time than N_2O, that the analysis is relatively simple and that as 4AA is a solid, it is not necessary to use anaerobic sampling procedures. The authors did not indicate how many goats were used in the study. A variety of general and spinal anesthetics was employed and it is apparent that the experiments were performed sporadically over a period of years. The uterine blood flow was reported to be 277 (sd 74) ml. per kilogram of uterine and intrauterine tissue at 70 days of gestation and did not change from that time to term.

This raises the question of the units in which uterine blood flow should be expressed. Metcalfe et al. (61) use ml. per kilogram of fetus per minute; therefore their value of 283 is lower than the

277 ml. per kilogram of uterus and intrauterine tissue. Presumably these tissue weights are wet weights although neither group of authors consider it necessary to describe how these measurements were made, nor do they provide information whereby the results of the flow determinations can be compared to those obtained by other workers. It is obvious that if a uterine blood flow reported to be 283 ml. per kg. tissue per min. is to be of any value, then the mean tissue weight must also be reported. Comparisons of this results with previously published figures for flow per kg. fetal tissue per min. can only be made if the mean tissue weight is broken down into fetal weight, placental weight and uterine weight. It is unfortunate that the usefulness of this experiment is compromised by inadequate reporting.

In a later review Huckabee (40) discusses this work and claims to be able to obtain repeated measurements of uterine blood flow in unanesthetized resting animals over a period of months. In support of this statement he presents a figure illustrating the measurement of serial uterine blood flows in an unanesthetized sheep purportedly reproduced from the article just reviewed (reference 41). This is a gross misrepresentation of the facts. This figure does not appear in the specified article and, as has been mentioned, the article concerns single determinations of uterine blood flow in anesthetized goats not serial determinations in unan-

esthetized sheep. There is no basis in the literature for Huckabee's claim.

Kirschbaum et al. (48) demonstrated the usefulness of the electromagnetic flowmeter in the measurement of uterine blood flow. Details of the technique are described in a separate publication (17). The disadvantage is that there are at least 4 arteries serving the uterus, two caudal uterine arteries and two ovarian arteries (8). The measurement of flow in one of these vessels does not provide a value for the total uterine blood flow. Kirschbaum et al. double the flow rates observed in a single uterine artery and report uterine blood flows of 268 to 288 ml. per minute per kilogram of fetal weight, in the near term sheep. Here again, the values for mean fetal weight are not given. These authors compare this figure directly with the value of 277 obtained by Huckabee et al.(41) apparently unaware that the latter is based on the total tissue weight of the uterus and contents and is therefore considerably greater than Kirschbaum's estimate. The main objections to measuring the flow in one umbilical artery are that the presence of the flowmeter head may lower the flow in that vessel by inducing vascular constriction and that the contribution from sources other than the two caudal uterine arteries is neglected. Both of these disadvantages would result in an erroneously low estimate of uterine blood flow.

The measurement of umbilical blood flow presents differ-

ent problems and requires different techniques. Efforts to measure umbilical flow have on the whole been more successful than attempts to measure uterine blood flow. This is largely due to the fact that the whole of the umbilical flow, in the sheep and goat, is contained in two long pairs of arteries and veins in the cord. These vessels are large and easily accessible through an incision in the uterus. In addition the umbilical veins fuse as they enter the abdomen of the fetus providing a short length of vessel through which all of the umbilical flow must pass. These anatomical features facilitate the acquisition of representative blood samples for flow determinations.

Barcroft (6) describes the first attempts to measure umbilical blood flow, but the first reasonable successful technique was developed by Cooper and Greenfield (21) who totally immersed a fetal lamb in a bath of warm saline, arranged as a plethysmograph, while retaining the integrity of the umbilical circulation. When the umbilical veins were occluded, the rate of decrease of fetal volume was taken to represent the umbilical flow. With this technique, Cooper, Greenfield and Huggett (22) reported the umbilical flow in the near term lambs to be 500 ml. per minute. Acheson, Dawes and Mott (1) obtained corroborative results in 1957 and the method has even been applied to the human fetus (31) in the first successful direct measurement of human umbilical blood flow. In a recent review (24) Dawes pointed out that the method was subject to several

errors, all of which tend to underestimate flow.

In 1964 Dawes and Mott (25) published the results of a series of experiments in which the umbilical blood flow in near term lambs was measured directly with an electromagnetic flowmeter. The flowmeter head was inserted into a short external circuit interposed between the cut ends of the abdominal umbilical vein. Observations were made on ten lambs at 137-141 days of gestation, delivered by Caesarean section. In the course of this procedure the umbilical circulation was totally occluded for two minutes. They reported the umbilical blood flow to be 170 (sem 14) ml. per kilogram of fetus per minute. The mean fetal weight was 4.22 ± 0.31 kg. so that the absolute umbilical blood flow in these lambs was 717 ml. per minute, which is higher than the values obtained by plethysmography as Dawes had predicted. In a similar experiment, Kirschbaum et al. (48) reported the mean umbilical flow in eight near term fetal lambs to be 183 (sd 56) ml. per kilogram of fetus per minute, which is essentially the same as the values obtained by Dawes and Mott (25).

Meschia et al. (56) measured the umbilical blood flow in sheep on the Fick principle, using urea as the test substance. They reported that the umbilical blood flow in fetuses greater than three kilograms in body weight, was 178 ml. per kilogram per min. The values ranged from 152 to 212 ml. /kg. per min. The mean

fetal weight was 3.41 kg. and the mean absolute umbilical blood flow was 609 ml./min. This experiment led to the development of a method for the simultaneous determination of umbilical and uterine blood flows which has been successfully used by Meschia et al. to provide definitive measurements of these quantities (57).

Basically the method is a special application of the Fick principle. A test substance was infused at a known rate into the umbilical vein. Sampling catheters were placed ten centimeters upstream from the infusion catheter in the umbilical vein, in an umbilical artery and in a uterine vein and carotid artery. After 40 mins. of infusion the initial phase of accumulation was completed and blood samples were taken at one minute intervals.

The infusion rate was known hence the umbilical flow was equal to the infusion rate of indicator divided by the umbilical arterial to venous concentration difference. The simultaneous uterine blood flow was equal to the infusion rate of indicator divided by the uterine venous to arterial concentration difference. These calculations are only valid if the amount of test substance infused is equal to the transplacental loss from the fetal side which must also equal the transplacental gain in the maternal side. Proof that the samples satisfy this criterion was afforded by plotting sample concentration versus time. In the steady state this should result in two pairs of roughly parallel lines, the slopes of the lines

indicating the rate of accumulation of the test substance in the mother and fetus. Antipyrene was used as the test substance and the authors report that it is non-toxic at analyzable concentrations, highly soluble in water, slowly metabolized, rapidly diffusible across biological membranes and bound only in small amounts to other plasma constituents.

An experiment such as this generates many samples and a method was developed to analyze antipyrene automatically in 0.4 ml. plasma samples by means of a Technicon Autoanalyzer. The plasma concentration of dialyzable antipyrene was converted to blood concentration by means of empirical equations derived from in vitro studies on adult and fetal blood. Some antipyrene was excreted and metabolized by the fetus. The rate at which this occurred was measured in ten fetuses and found to be less than three per cent of the infusion rate.

The authors used six sheep and ten goats between the 100th and 140th day of gestation. Complete data were presented for each experiment. The mean umbilical blood flow was 233 (sem 19) ml. per kg. fetal weight per minute, the mean fetal weight was 1.79 kg. and the mean absolute umbilical blood flow was 416 ml./min. The mean uterine blood flow was 276 (sem 28) ml. per kg. of uterus and intrauterine tissue, with a mean uterine plus intrauterine tissue weight of 2.87 kg. The mean absolute

uterine blood flow was therefore 791 ml./min. These data permit the calculation of the ratio of the umbilical to uterine flow for each conceptus. These values ranged from 0.192 to 1.43. The uterine blood flows reported here by Meschia et al. agree with the estimates of Huckabee et al. (41) but their figure for umbilical blood flow is higher than that reported by Dawes and Mott (25). Rudolph and Heymann (75) checked the validity of the antipyrene double flow method with simultaneous flowmeter measurememts of umbilical flow in nine fetal lambs. They found that the antipyrene concentration was the same in both umbilical veins thereby justifying the single umbilical venous sampling catheter. They also report that all but two out of twenty-five observations of umbilical blood flow recorded by the two methods fell within the $\pm$ 10% of the line of identity.

Meschia et al. (57) thought that their estimates of umbilical blood flow were higher than those reported by Dawes and Mott (25) because the latter group delivered the fetus before making the measurement and that this procedure caused a decrease in umbilical flow. Rudolph and Heymann consider their results to have supported this conclusion and that delivering the fetus does cause a decrease in umbilical blood flow.

A variety of methods have been described for the measurement of uterine and umbilical blood flow. The results

generated by these techniques do not conflict when it is realized that these flows need not be constant. The fact that these flows are sensitive to anesthesia and surgical intervention must be borne in mind when interpreting the results of an experiment.

The bulk of the literature pertaining to placental hemodynamics suffers from the fact that many authors have set out to measure the quantity, be it pressure, volume, or flow, without any real appreciation of why the measurement is necessary. The consequence of this is that there are a great many observations made under a variety of conditions. It is clear that many of these observations have been made with no other aim than to make the measurement. These data would have been more useful had they been acquired in the course of answering a question pertaining to some physiological problem which related to the phenomenon of pregnancy. It is unlikely that measurements made because the quantity is there to be measured can be of much use in providing an answer to the question of why the quantity is there.

PLACENTAL EXCHANGE OF RESPIRATORY GASES

The descriptive studies concerned with vascular architecture and hemodynamics have been considered in previous sections. In addition to these two problem areas the understanding of the physical characteristics of the placenta requires the

measurement of one further parameter, that is, the resistance offered by the tissue between the two blood streams to diffusion. This measurement requires that the amount of a substance that crosses the placenta in a known period of time be related to the pressure or concentration gradient that is causing the transfer. The most convenient substance to use for this purpose is one which normally is crossing the placenta. In this context many observations have been made of the placental transfer of respiratory gases. The calculations necessary to these studies are quite complex and several simplifying assumptions have been adopted. The various techniques that are used to predict the physical characteristics of the placenta from observations of respiratory gas transfer will be explained. Results obtained from experiments in which these techniques have been used will be evaluated and the limitations imposed by the assumptions upon the usefulness of such results will be emphasized.

Respiratory gases are not present in blood in physical solution only. Some oxygen is reversibly bound to hemoglobin. The relationship between the partial pressure of oxygen and its concentration is expressed by the familiar oxygen dissociation curve. Carbon dioxide is present in blood as bicarbonate ion, undissociated carbonic acid, carbaminohemoglobin, and dissolved carbon dioxide. Thus CO_2 could diffuse across the placenta in any

one or all of these three forms. For this reason the analysis of placental function using carbon dioxide would be difficult and oxygen has generally been selected as the most convenient respiratory gas for the examination of placental function.

The analysis of placental function by the use of oxygen requires that the relationship between the partial pressure of oxygen and the oxygen concentration in blood be established. This requires two additional items of information, the hemoglobin concentration and the plasma pH. A nomogram of the maternal and fetal oxygen dissociation curves for goat blood relating percentage saturation, pH and P_{O_2} is given by Hellegers et al. (39). The analysis of oxygen transfer across the placenta of the sheep is further complicated by the presence of two electrophoretically distinct hemoglobin types in the adult (36). In this species it is also necessary to know the hemoglobin type before converting P_{O_2} to oxygen concentration (64).

The study of oxygen transfer across the placenta would be greatly simplified if it could be proved that oxygen moves across the placenta by a process of passive diffusion and that there is no active secretion of this gas. Huggett (42) presented such a proof in 1927. He immersed anesthetized near term goats in a bath of warm saline. The fetus was delivered into the bath via abdominal and uterine incisions. The head of the fetus was kept below the

surface of the saline throughout the experiment. Cannulae were placed into an umbilical artery and an umbilical vein. Huggett first showed that the P_{O_2} in the uterine artery was higher than that in the umbilical artery thus establishing the existence of an oxygen pressure difference that would permit diffusional exchange from mother to fetus. He then rendered the mother hypoxic and observed a marked inhibition of the maternal to fetal oxygen transfer. Huggett concludes that this effect would be unlikely to occur if oxygen were secreted whereas it is easy to understand on a diffusion hypothesis. This is sparse evidence on which to base so sweeping a conclusion. Meager corroboration is provided by Campbell et al. (20) who perfused the fetal side of the sheep placenta with a mechanical pump. They found that the transplacental oxygen gradient could be reversed and that oxygen could move from the fetal to the maternal side.

In summary, there is no direct evidence that oxygen is secreted by the placenta but the evidence that oxygen is not so secreted is unconvincing. This is a problem area that has attracted little interest and all further studies on placental oxygen transfer, that will be discussed in this section, assume that there is no active component to oxygen transfer across the placenta.

The accepted approach to the study of placental oxygen transfer has used concepts derived from the study of pulmonary

diffusion, a field which has been highly developed and refined (30). This approach consists of applying the Fick diffusion equation in the form:

$$\dot{V}_{O_2} = K_{PO_2} A (\bar{P}_{MO_2} - \bar{P}_{FO_2})/L \quad (58)$$

where: $\dot{V}_{O_2}$ = The net rate of oxygen diffusion from mother to fetus.

K_{PO_2} = The placental diffusion constant for oxygen (ml./min. x cm. x mm. Hg).

A = The placental surface area (cm^2).

L = The average diffusion distance for oxygen (cm.).

$\bar{P}_{MO_2}$ = The average oxygen tension in the maternal placental bed (mm. Hg).

$(\bar{P}_{MO_2} - \bar{P}_{FO_2})$ = The integrated mean oxygen pressure difference across the placenta, i.e., that oxygen pressure difference which, if maintained along the entire length of the capillaries, would cause the same rate of oxygen transfer as actually diffuses across under biological conditions. In practice K_{PO_2}, A and L are combined to form $D_{PO_2} = K_{PO_2} A / L$ where D_{PO_2} is the diffusing capacity of the placenta and $D_{PO_2} = \dot{V}_{O_2} / (\bar{P}_{MO_2} - \bar{P}_{FO_2})$.

The diffusing capacity of the placenta can be determined either from the diffusing constant, the area and the mean diffusing distance or from the net rate of oxygen transfer and the mean oxygen pressure gradient. Metcalfe, Bartels and Moll (58) point out that the former

calculation is not very useful because estimates of K_{PO_2}, A and L are difficult to obtain. Some approximations of these values that could be used to calculate D_{PO_2} for the goat placenta are as follows:

$K_{PO_2} = 2 \cdot 7 \times 10^{-7}$ cm^2 / sec atm. (The value for muscle tissue (49).)

$A = 4 \times 10^4$ cm^2 (The value for the 112 day goat placenta (43).)

$L = 3 \cdot 5 \times 10^{-4}$ cm. (The value for the human placenta (2).)

On the basis of these figures

$$D_{PO_2} = 2 \cdot 4 \text{ cm}^3 \text{ / min. mm. Hg}$$

This quantity is often expressed per kilogram of fetus so that for a 2 kg. fetus $D_{PO_2} = 1 \cdot 2$ ml. per (min. x mm. Hg x kg. fetal weight.) These figures are not very reliable and the calculation of D_{PO_2} from measurements of $\dot{V}_{O_2}$ and $(\bar{P}_{MO_2} - \bar{P}_{FO_2})$ has been considered more profitable.

The net placental oxygen transfer $\dot{V}_{O_2}$ has been calculated from the umbilical venous to arterial concentration difference times the umbilical blood flow. Dawes (24) reported this value to be 4 to 6 ml. O_2/ kg. fetus per min. in the near term lamb. Meschia et al. obtained a value of 6·3 ml. /kg. fetus per minute in mature lambs (56) but in a later work with sheep and goats, Meschia's group raised this figure to 7·1 ml. /kg. fetus per minute (57).

The net oxygen transfer across the placenta has also been assumed to equal the uterine arterio-venous oxygen difference times

the uterine blood flow (58). Meschia et al. (57) report the uterine oxygen uptake in sheep and goats to be $9 \cdot 9 \pm 0 \cdot 4$ ml./kg. of uterus plus contents per min., at term.

The calculation of the mean oxygen pressure gradient is more complex. Barron and Alexander (11) developed a technique that required knowledge of the maternal and fetal oxygen dissociation curves, the oxygen pressures in the umbilical and uterine arteries and veins, and the vascular architecture. The method employed a graphical construction of the oxygen pressure drop along the exchanging capillaries which in the sheep placenta were assumed to be in a countercurrent configuration. By this method $(\bar{P}_{MO_2} - \bar{P}_{FO_2})$ was reported to be close to 43 mm. Hg in the near term sheep. The method was modified by Barron and Meschia in 1954 (12) and in 1954 Lamport (50) published a more sophisticated procedure based on the same concepts. Lamport's estimate of $(\bar{P}_{MO_2} - \bar{P}_{FO_2})$ in the sheep is the same as that of Barron and Alexander. In a recent review Metcalfe et al. (58) calculated the diffusing capacity for oxygen of the sheep placenta using data taken from the literature. They gave a value $0 \cdot 2$ ml. of O_2/kg. fetus per min. per mm. Hg pressure difference, assuming a countercurrent capillary configuration. These authors pooled several sources of information and reported the mean oxygen partial pressure difference across both the sheep and goat placenta to be 40 mm.

Hg when a countercurrent configuration is assumed.

Barron and Alexander (11) and Barron and Meschia (12) report that the placental diffusing capacity for oxygen in the sheep was between 0·1 and 0·2 ml. per (min. x mm. Hg x kg. fetal weight). In addition Bartels and Moll (16) using independent methods arrived at essentially the same figure, 0·1 ml. per (min. x mm. Hg x kg.) in the human placenta. The oxygen consumption of the fetal goat was found to be the same as that of the sheep (57) and given the same mean oxygen tension gradient for the two species then D_{PO_2} for the goat placenta is the same as that for the sheep and is between 0·1 and 0·2 ml. per (min. x mm. Hg x kg. fetal weight). This is one order of magnitude less than the value of 1·2 ml. per (min. x mm. Hg x kg. fetal weight) for D_{PO_2} calculated from the diffusional coefficient, area and thickness which is very good agreement considering the inaccuracy that must invade the measurement of these latter quantities.

A major consideration that has largely been evaded in the past is that the measurement of D_{PO_2} is not very useful in itself, but can only be of real value if the answer can be used to predict the effect of a change. Only one group of workers have taken the trouble to check the validity of the equations used to calculate D_{PO_2} to see if they do predict the effect of a change in one of the relevant variables. Kirschbaum et al. (48) pointed out that if the equation used

to calculate D_{PO_2} is valid as applied to the placenta, then certain predictions could be made as to what would happen if the maternal blood oxygen concentration were increased. The equation is:

$$\dot{V}_{O_2} = D_{PO_2} (\bar{P}_{MO_2} - \bar{P}_{FO_2})$$

and D_{PO_2} as a physical property of the placenta would remain constant hence the result of maternal hyperoxia would be:

1. A transient increase in $\dot{V}_{O_2}$.
2. A secondary increase in $\bar{P}_{FO_2}$.
3. The attainment of a new $\dot{V}_{O_2}$ at a new steady state of concentrations.
4. An increase in the partial pressure of oxygen on the fetal side of the system proportional to the increase in the partial pressure of oxygen on the maternal side.

The authors used 21 near term sheep under spinal anesthesia and administered 100% O_2 for one hour after a one to two hour control period. A final control period of one hour terminated each experiment. They found that increasing the maternal arterial P_{O_2} above normal values had the following results:

1. If a transient increase in net oxygen transfer occurred, it was not detectable 30 minutes after the onset of oxygen breathing.
2. A secondary increase in oxygen partial pressure was seen as predicted, both in umbilical arterial and venous blood.

3. A new $\dot{V}_{O_2}$ was observed during hyperoxia but it was lower than the control rate, a fact that was not predicted. The lower $\dot{V}_{O_2}$ returned to normal during the final control period.

4. A proportional increase in fetal blood P_{O_2} did not occur during hyperoxia. The P_{O_2} of the fetal blood appeared to be held below values of 60 mm. Hg.

Kirschbaum et al. consider that the failure of the equation to predict the effect of maternal hyperoxia renders it an unsatisfactory model for placental oxygen diffusion and that the values of D_{PO_2} obtained from its application are of questionable value.

At the same time Longo et al. (51) measured the diffusing capacity of the sheep placenta for carbon monoxide (D_{PCO}). The method had the advantage that the mean maternal-fetal P_{CO} difference was constant along most of the length of the capillary, hence $\bar{P}_{MCO}$ and $\bar{P}_{FCO}$ were equal to the measured CO concentration in the uterine and umbilical veins respectively. These authors used ten near term ewes under spinal anesthesia supplemented with barbiturate anesthesia. The rate of CO transfer across the placenta ($\dot{V}_{CO}$) was given by formula:

$$\dot{V}_{CO} = \frac{D\ (COHb)_F \times \text{capacity} \times \text{CO "space"} \times F}{100 \times \text{minutes}}$$

where $D\ (COHb)_F$ is the change in the concentration of carboxyhemoglobin during the period of time under consideration, capacity is

the hemoglobin concentration times 1 · 34 and the CO "space" F is the change in total CO in the fetus divided by the change in the blood CO concentration. By this means Longo et al. found that D_{PCO} was 0 · 54 ml. per (minute x mm. Hg x kg. fetal weight) (sd $\pm$ 0· 13) in the near term sheep placenta. They further pointed out that the relative rates of reaction of O_2 and CO with red cell hemoglobin and the relative rates of diffusion of the two gases suggest that the true D_{PO_2} should be 1 · 2 to 2 times greater than the D_{PCO} or 0· 65 to 1 · 1 ml. per (minute x mm. Hg x kg. fetal weight). This is about five times greater than values obtained from measurements of P_{O_2} in the mixed uterine and umbilical blood. Longo et al. also stressed that if the D_{PO_2} is between 0 · 65 and 1 · 1, as their results indicated, then the maternal and fetal placental end capillary P_{O_2} gradients that are observed in the sheep placenta are caused by factors other than a diffusional barrier to placental oxygen transfer.

The results presented by Kirschbaum et al. and Longo et al. provide strong evidence that D_{PO_2} is an unsatisfactory quantity to measure. Previous workers were not measuring D_{PO_2} at all but the effect of several factors on the umbilical and uterine venous P_{O_2} that were not taken into account in the calculation of D_{PO_2}. It is apparent that the early work of Barcroft and Barron (8) ostensibly proving that the sheep placenta was a countercurrent exchanger was accepted too readily. The concept of countercurrency meant that if oxygen dif-

fused freely across the placental membrane then the umbilical venous P_{O_2} would have to be higher than the uterine venous P_{O_2} and in fact tend towards the maternal arterial P_{O_2}. The fact that measurements of the umbilical venous P_{O_2} were always lower was explained by the presence of a barrier to the diffusion of oxygen, hence the D_{PO_2} could be measured. The work of Longo et al. and Kirschbaum et al. indicate that D_{PO_2} cannot be measured, that reported values for D_{PO_2} are not valid and that oxygen equilibrates across the placental membrane with little or no end capillary oxygen gradient. It is apparent that the oxygen pressures observed in uterine and umbilical venous blood are not representative of end capillary oxygen pressures and that oxygen cannot be used to examine placental function directly. The apparent end capillary oxygen gradient observed in the placental venous outflows are due to the effect of several factors not considered in the classical calculation of D_{PO_2}. What these factors may be is discussed in the next section.

THE PLACENTA AS A SIMPLE EXCHANGER

In the preceding section we considered the use of respiratory gases in the analysis of placental function. Much data are available on oxygen pressures and contents on both sides of the placenta but the expression of these data in the form of placental diffusing capacity or mean oxygen tension gradient appears to be meaningless. The

assumptions necessary for applying to placental physiology the techniques which have proved useful in studies of pulmonary physiology will be considered in this section. If the basic assumptions are found to be invalid, then it will not be possible to examine placental function with these techniques and new approaches must be developed. Much of the work that will be discussed is very recent. One of the most significant changes that is presently occuring is a developing awareness of the inadequacy of the established methodology in the field of placental exchange. The direct result of this awareness is a breaking away from the conventional approaches and the development of original concepts that have not yet had time to become firmly established. The subject is in a state of flux and in this section some of the results of this recent upheaval will be discussed.

The critical assumptions made in the calculation of D_{PO_2}, $(\bar{P}_{MO_2} - \bar{P}_{FO_2})$ and $\dot{V}_{O_2}$ are as follows:

1. The architecture of the exchanging capillaries is known.

2. The permeability is evenly distributed within the exchanging area; i.e., the diffusional resistance between any two adjacent maternal and fetal capillaries is uniform for all pairs.

3. The umbilical and uterine venous blood samples are representative of blood leaving the exchanging capillaries; i.e., all of the maternal and fetal flow goes to the exchanging area and none is

shunted through non-exchanging areas.

4. There is no oxygen consumption within the utero-placenta tissue itself. The umbilical or uterine arterio-venous oxygen difference multiplied by the umbilical or uterine blood flows respectively are equal to the net placental transfer of oxygen.

5. The maternal and fetal blood flows are evenly distributed within the exchanging area; i.e., the ratio of the flows in any adjacent maternal and fetal capillary is the same in all adjacent maternal and fetal capillaries.

6. There is a measurable end-capillary oxygen pressure difference; i.e., equilibration occurs during the passage of the blood through the maternal and fetal capillaries but is never complete.

Most of these assumptions are summarized by Lamport as follows:

> "The placenta can be adequately represented by two single vessels each of uniform (though not the same) bore, equal in length, and separated by intervening tissue such that the rate of gas diffusion from any point of one vessel to the other is proportional to the pressure gradient of the gas dissolved in the blood within the two vessels at the point of contiguity, the constant of proportionality being everywhere the same." (50)

The validity of these assumptions will be considered in order.

1. The vascular anatomy of the sheep placenta has been considered in detail. It is unlikely to be a pure countercurrent or con-

current exchanger but a mixture of the two. Lamport's method has not been modified to handle this type of exchanger and it is unlikely that the integrated mean oxygen pressure gradient can be calculated.

2. The anatomical evidence indicates that the distance between the maternal and fetal capillaries is not constant but varies widely over the whole placenta. Wimsatt (84) explains that the anatomical classification is an oversimplification. He points out that

> "In many placentas we observe fetal capillaries indent or actively invade the trophoblastic layer which invests the chorionic villi....In consequence of these invasions parts of the placental membrane in epithelio-, syndesmo-, and endotheliochorial placentas may actually be no thicker nor involve any more layers than the barrier in many hemochorial placentas."

Wimsatt further explains that while anatomical requirements may be satisfied by the requisite number of tissue layers, the variations in thickness of these layers produces thin areas. For this reason the placenta may be considered to be physiologically heterogeneous.

3. There is considerable evidence, of a diversified nature, to indicate that some of the blood flowing past the tip of the venous sampling catheters did not flow through exchanging capillaries and that the blood samples drawn from these catheters are not representative of end capillary blood from the exchanging area.

With respect to the fetal side of the placenta, Metcalfe et al. (59) developed a method to test the hypothesis that umbilical venous

blood was contaminated with blood from non-exchanging areas. They reasoned that if a solution containing no hemoglobin, but saturated with carbon monoxide (CO) was pumped into the umbilical arteries towards the placenta, then all of the perfusate that passed through the exchanging area would have the CO completely removed. This would occur because the hemoglobin in the adjacent maternal blood would bind the CO to form carboxyhemoglobin. The partial pressure of CO in the maternal capillaries would always be close to zero. The solubility of CO in aqueous solution is very low

(aCO = 0 · 0188 vol gas STP/vol liquid at 1 atm partial pressure (13))

and the combination of a high partial pressure difference with a small quantity to be moved across the placenta should result in all of the CO being transferred from the fetal to the maternal side. If any of the perfusing fluid did not pass through the exchanging capillaries, it would retain all of its CO, once equilibration with the tissues was achieved. It is apparent that the concentration of CO in the venous effluent divided by the concentration of CO in the arterial inflow would be equal to the fraction of the flow that did not pass through the exchanging area. This fraction is referred to as the shunted flow or fetal shunt. Metcalfe et al. used Krebs solution containing 10% of dextran as the perfusing fluid. They made 20

determinations of the fetal shunt in nine sheep and report a mean value of 19% (sd 3%).

There are many objections to this technique which were not considered by the authors. Complete removal of CO from the non-shunted flow was not proven and it is unlikely that the venous outflow was hemoglobin free. The presence of residual hemoglobin in the effluent would bind the CO on the fetal side and invalidate the technique. The most serious criticism is that during the perfusion, the tissues adjacent to the exchanging area would receive oxygen from the maternal blood by diffusion but the tissues served by the shunt flow would be completely hypoxic. It is unlikely that the proportion of flow being shunted during this period of tissue hypoxia would be the same as in the normal state of tissue oxygenation.

Independent support is given to the technique by Meschia et al. (54) who published a graph of umbilical flow ($\dot{Q}_F$) over antipyrene clearance (C_A) versus the ratio of umbilical to uterine blood flow (R^M). The antipyrene clearance is defined as the quantity of antipyrene crossing the placenta per minute ($\dot{q}$) divided by the arterial concentration difference for antipyrene ($C_{FA} - C_{MA}$). At a flow ratio of 0, the value of $\dot{Q}_F/C_A$ was 1 · 25. The data were obtained from the experiments (57) earlier described in the section on placental hemodynamics. From the definition of C_A we have

$$\dot{Q}_F/C_A = \dot{Q}_F (C_{FA} - C_{MA}) / \dot{q}$$

By the Fick principle

$$\dot{q} = \dot{Q}_F (C_{FA} - C_{FV})$$

Therefore

$$\dot{Q}_F / C_A = (C_{FA} - C_{MA}) / (C_{FA} - C_{FV})$$

If there is a fetal shunt as Metcalfe et al. suggest, then the measured concentration of antipyrene in the fetal vein C_{FV}, is equal to the fraction shunted S_F, times the concentration of antipyrene in the fetal artery, plus the rest of the umbilical flow times the concentration in representative end fetal capillary blood C_{FV}*; i.e.,

$$C_{FV} = S_F C_{FA} + (1 - S_F) C_{FV}^*$$

As the flow ratio tends to zero, the maternal venous-arterial antipyrene concentration difference becomes less and less, tending to zero and the fetal end capillary concentration of antipyrene tends to approach the maternal arterial antipyrene concentration; i.e.,

$$\lim_{R \to 0} \quad C_{FV}^* = C_{MA}$$

and

$$\lim_{R \to 0} \quad C_{FV} = S_F C_{FA} + (1 - S_F) C_{MA}$$

Therefore

$$\lim_{R \to 0} \quad (C_{FA} - C_{FV}) = (1 - S_F)(C_{FA} - C_{MA})$$

so that

$$\lim_{R \to O} \quad (C_{FA} - C_{MA}) / (C_{FA} - C_{FV}) = 1 / (1 - S_F)$$

The value of the ratio of umbilical flow to antipyrene clearance at R = O is therefore equal to $1/(1 - S_F)$.

From the graph given by Meschia et al.

$$1/(1 - S_F) = 1 \cdot 25$$

Therefore, $S_F = 0 \cdot 2$; i.e., the fetal shunt is 20% in the near term sheep. This value is not different from the value of 19% given by the CO perfusion technique. Meschia's data were obtained from a preparation with an intact fetal circulation and as such provides evidence that the CO technique is valid. This permits the conclusion that there is a fetal shunt in the near term lamb and that this shunt is of the order of 20% of the umbilical blood flow.

The evidence for the presence of shunts on the maternal side is less direct but nevertheless convincing. Elliott Hall and Huggett (26) found that the weight of the near term goat uterus was about 500 grams. It is possible that this mass of tissue could receive its oxygen supply by back diffusion from the exchanging area but more probable that it has its own blood supply separate from that of the exchanging area of the placenta. This myometrical flow is drained into the uterine veins that are sampled with a uterine venous catheter and would therefore constitute a maternal shunt.

Steven (79) has demonstrated the presence of large arteriovenous anastomoses in latex casts of the sheep placenta which would contribute shunted blood to the maternal veins. Longo et al. (51) pointed out that oxygen introduced by shunting into the calculation of D_{PCO} was much less than that for D_{PO_2}. The D_{PO_2} predicted from the D_{PCO} found by Longo's group was not the same as that found by direct determinations of D_{PO_2}. This means that whatever interfered with the direct determination of D_{PO_2} did not interfere with the determination of D_{PCO}. A possible source of this interference would be the presence of maternal and fetal shunts. These pieces of evidence are not conclusive but taken together they provide inferential support to the suggestion that some of the uterine blood is shunted away from the exchanging area.

4. The evidence for uteroplacental oxygen consumption is strong. More oxygen is lost from the uterine blood flow than is gained by the umbilical blood flow yet it appears certain that neither the oxygen lost from the uterine blood nor the oxygen gained by the umbilical blood is equal to the amount of oxygen that crosses the placenta.

Meschia et al. (57) found that the oxygen uptake of the fetus in near term sheep and goats was in many cases equal to the oxygen uptake of the utero-placental tissue. Faber and Hart (28) found that 30% of the oxygen that was extracted from the uterine blood flow of

the rabbit did not appear in the umbilical circulation. The placenta is therefore consuming some of the oxygen that is diffusing from the maternal to the fetal side. The calculation of D_{PO_2} requires a knowledge of the amount of oxygen crossing the placenta ($\dot{V}_{O_2}$). The evidence cited indicates that the amount of oxygen extracted from the uterine blood ($\dot{V}_{O_2}M$) is equal to the amount crossing the placenta ($\dot{V}_{O_2}$), plus the amount consumed in the uterine myometrium ($\dot{V}_{O_2}U$). The amount of oxygen that appears in the umbilical circulation ($\dot{V}_{O_2}F$) is equal to that amount which crossed the placenta ($\dot{V}_{O_2}$) minus the amount that was consumed in the fetal placental tissue ($\dot{V}_{O_2}P$). The quantity that is required, $\dot{V}_{O_2}$, has never been measured because $\dot{V}_{O_2}P$ and $\dot{V}_{O_2}U$ have never been measured.

5. The existence of an uneven distribution of maternal and fetal flows within the placenta has been suspected (51) but a preparation that would permit the detection and measurement of this phenomenon has only recently been developed. In 1963 Ramsey et al. (52) observed intermittent surging and blanching of the maternal placental circulation of the primate placenta and in 1966 Martin et al. (53) observed the same phenomenon in the fetal placental circulation.

Positive proof that the maternal and fetal blood flows were not evenly distributed throughout the placenta was afforded by Powers et al. (71) in 1967. They injected macroaggregates of albumin

(MAA) labelled with radioactive isotopes into the fetal and maternal arterial circulations of pregnant sheep. The MAA in one circulation was labelled with I^{125} and the MAA in the other circulation labelled with I^{131}. The energy spectra of these two isotopes were sufficiently distinct to enable one isotope to be counted in the presence of the other. The MAA were assumed to lodge and remain in small placental vessels without causing gross hemodynamic alterations. After the injection of MAA, the uteroplacental tissue was removed and scanned with a scintillation counter. Samples of tissue were then taken at random from cotyledons and full thickness sections were cut. These sections were counted for I^{125} and I^{131} in a well-type scintillation counter.

The authors found that the distribution of maternal placental flow was uneven among the cotyledons as well as within a given cotyledon. Fetal blood flow was also distributed non-uniformly among and within the cotyledons. The ratio of maternal to fetal placental flow could have remained constant in spite of the uneven maternal and fetal distributions but Powers et al. found that this ratio varied over the surface of the placenta.

The observations of Ramsey et al. and Martin et al. suggested that the pattern of distribution of blood flow to the placenta may not be fixed, but may be changing with time. The MAA technique of Powers et al. which measured the pattern of flow distri-

bution as it was when the MAA lodged in the vessels does not give any information about the possibility of changes that may occur. To test this Powers et al. rendered the ewe hypoxic by administering 10% O_2. They found that maternal and fetal placental flows became more evenly distributed throughout the placenta and that the ratio of the maternal to fetal placental flows also became less variable, as compared to the control observations. When an umbilical artery was ligated during air breathing, the flows to the remaining two thirds of the placenta again became less variable as compared to the control observations. These results indicate that both the uterine and the placental flows in the near term placenta are very unevenly distributed over the placental surface and that there is a mechanism whereby the distribution can be changed to regulate the effectiveness of the placenta as an exchanger.

6. The theory of a diffusional block to placental oxygen transfer has been based on the assumption that the sheep placenta is a countercurrent exchanger and on the observation of what appear to be end-capillary oxygen tension differences. The evidence for the countercurrent hypothesis has been discussed and found to be inadequate. An apparent end capillary oxygen tension difference could be explained on the basis of shunting but is more clearly attributable to unevenly distributed blood flows. Meschia et al. (54) present a proof, based on a series expansion, that the uneven distribution of

flow ratios must lead to apparent end-capillary concentration differences when there are no concentration differences at the ends of each pair of capillaries. Power and Longo (70) have calculated the contribution of unevenly distributed flows to the observed uterine venous to umbilical venous oxygen tension difference in a sheep placenta assumed to resemble a concurrent exchanger. They found that 10 mm. Hg of the normal uterine venous to umbilical venous P_{O_2} difference of 15 mm. Hg, was due to the uneven distribution of the maternal and fetal blood flows in the near term sheep. They conclude that this factor is the principal limitation to placental oxygen exchange. These results indicate that placental oxygen transfe. need not be diffusion limited and that the equilibration of oxygen is probably complete at the venous ends of the placental capillaries. The apparent end capillary oxygen tension gradient is probably a function of shunted and unevenly distributed maternal and fetal placental blood flows.

The preceding discussion indicates that none of the assumptions necessary to the placental application of techniques basic to pulmonary physiology is valid. This being the case, it appears to be pointless to attempt to measure the placental diffusing capacity or the mean oxygen pressure gradient across the placenta. The placenta poses its own unique problems. Techniques to examine placenta function must be developed with an awareness of these

problems.

PREDICTED MODEL BEHAVIOR

The search for more effective techniques to apply to the examination of placental function has prompted several investigators to attempt a more sophisticated mathematical approach to placental exchange. Wilkin (82), Bartels and Moll (16), Faber and Hart (28), and Meschia et al. (54) have all compared the placenta to various simple exchangers. The large body of information pertaining to the theory of heat exchangers can be applied to the analysis of placental function when specific analogies are described. This approach should be especially useful in the description of the predicted behavior of model systems. The equations defining the behavior of various types of heat exchangers are readily available in the engineering literature (45). The extraction of numerical solutions to the various equations is tedious and time consuming but texts such as Kays and London (45) present figures and tables of solutions. From such sources the behavior of a particular model operating under specific conditions can be rapidly described. In order to use these data to describe the behavior of a placenta, it is necessary to interrelate certain specific groups of variables commonly used to describe heat and mass transfer. Several authors (16, 54) have derived equations which define the behavior of a model placenta

without showing how the numerical solutions provided for the analogous heat exchanger can be applied.

This section will describe equations defining the behavior of simpler heat exchangers. The equation defining the exchanging characteristics of a placental model will then be derived and compared to the equation describing a heat exchanger of that particular type. The two equations will be compared. The required analogies will be described and it will be shown how the numerical solutions which refer to the heat exchanger can be applied to the placental model. The numerical solutions for the equations defining the behavior of various models will be given. It should be emphasized that the prediction of the exchange characteristics of a model placenta initially requires that several simplifying assumptions be made. In the previous section many of these assumptions were proven to be inapplicable to the placenta. This section will deal only with idealized models of the placenta but the description of the predicted behavior of these idealized models can be related to more realistic models of the placenta in the next section.

A. HEAT EXCHANGERS

For the conventional two-fluid heat exchanger, the parameters relating to heat transfer performance are defined by Kays and London (45) as follows:

U = overall conductance for heat transfer, Btu/ (hr ^{o}F ft^2 of A)

A = surface area on which U is based, ft^2

t_h, in) = hot fluid terminal temperatures ^{o}F
t_h, out)

t_c, in) = cold fluid terminal temperatures ^{o}F
t_c, out)

C_h = (Wc)h = hot fluid capacity rate, Btu/(hr ^{o}F) where W is the mass flow rate and c is the specific heat

C_c = (Wc)c = cold fluid capacity rate Btu/(hr ^{o}F)

$\dot{q}$ = heat transfer rate Btu/hr

The overall conductance U comes from an "overall heat transfer rate equation":

$$\frac{dq}{dA} = U \ (th - tc)$$

The reciprocal of U is an overall thermal resistance which has a number of series components.

These variables are too numerous to permit ready graphical descriptions of their relation. For this reason they are grouped into a smaller number of nondimensional parameters which do allow this representation. The nondimensional groupings in common use are:

EXCHANGER HEAT TRANSFER EFFECTIVENESS

(EFFECTIVENESS)

$$E = \frac{Ch\ (th,\ in - th,\ out)}{C_{min}\ (th,\ in - tc,\ in)} = \frac{Cc\ (tc,\ out - tc,\ in)}{C_{min}\ (th,\ in - tc,\ in)} \quad ---1$$

where C_{min} is the smaller of the Ch and Cc magnitudes.

NUMBER OF HEAT TRANSFER UNITS

$$Ntu = AU\ /\ C_{min} \quad ---------- \quad 2$$

CAPACITY RATE RATIO

$$= C_{min}\ /\ C_{max} \quad ---------- \quad 3$$

where C_{min} and C_{max} are, respectively, the smaller and larger of the two magnitudes of Ch and Cc. For several simple models, it is possible to express effectiveness E as a function of Ntu and C_{min}/C_{max}. The effectiveness (E) compares the actual heat transfer rate,

$$\dot{q} = C_h\ (th,\ in - th,\ out) = C_c\ (tc,\ out - tc,\ in)$$

to q_{max}, the thermodynamically limited, maximum possible heat transfer rate, defined as

$$\dot{q}_{max} = C_c\ (th,\ in - tc,\ in) \text{ if } C_c < C_h \text{ or}$$

$$C_h\ (th,\ in - th,\ out) \text{ if } C_h < C_c.$$

The number of heat transfer units Ntu is a nondimensional expression of the "heat transfer size" of the exchanger. When Ntu is small, the effectiveness E is low, and when Ntu is large, the effectiveness E approaches the limit imposed by flow arrangement and thermo-

dynamic considerations.

The various types of heat exchangers are described by Kays and London (45) by means of the following effectiveness - Ntu relations.

COUNTERCURRENT FLOW

$$E = \frac{1\text{-Ntu exp}(- \text{Ntu } (1 - C_{min}/C_{max}))}{1-(C_{min}/C_{max}) \text{ exp } (- \text{Ntu } (1-C_{min}/C_{max}))} \text{-------4}$$

CONCURRENT FLOW

$$E = \frac{1\text{-exp } (- \text{Ntu } (1 - C_{min}/C_{max}))}{1 - C_{min}/C_{max}} \text{ ----------5}$$

CROSS CURRENT FLOW

1. Both fluids unmixed.

This type of exchanger can be thought of as a two fluid streams crossing at right angles, each being broken up into a large number of separate flow tubes for passage through the exchanger. The analytic solution for this arrangement cannot be expressed in the closed form, but numerical solutions based on series expansion are available (45).

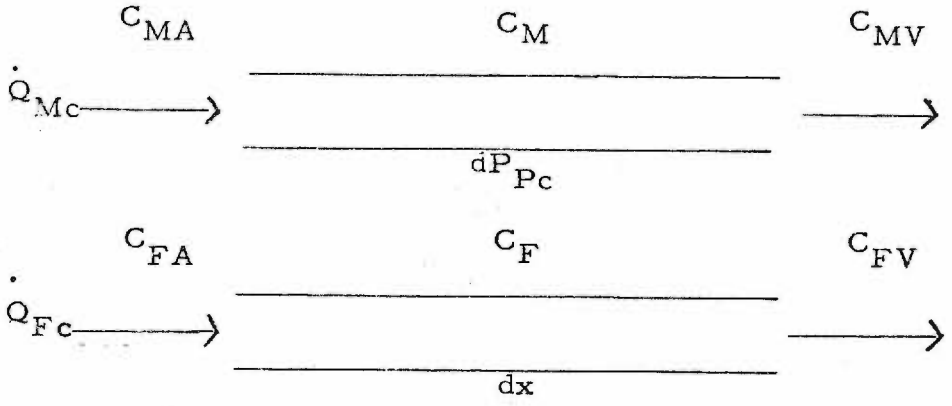
2. One fluid mixed, the other unmixed.

In this type of exchanger, one fluid is considered to flow through separate tubes so that cross mixing is nil, while the other fluid is perfectly cross mixed. Here again the solution cannot be

presented in closed algebraic form, but numerical solutions are available (45).

B. PLACENTAL ANALOGIES

We will now show how the equations describing the diffusional exchange of an inert substance, present only in physical solution in a placenta having concurrent flow. Equations 6 through 12 are a condensed version of Wilkin's analysis (82). The placenta will be represented by two parallel capillaries with the blood flow in each being in the same direction.



$\dot{Q}_{Mc}$ and $\dot{Q}_{Fc}$ are the respective blood flows in the maternal and fetal capillaries. C_{MA} and C_{MV} are the respective concentrations of the exchanging substance in the arterial and venous ends of the maternal capillary. C_{FA} and C_{FV} are the respective concentrations of the exchanging substance in the arterial and venous ends of the fetal capillary. C_M and C_F are the respective concentrations of the substance in the maternal and fetal capillaries at any point along their

length. dP_{Pc} is the permeability of a small segment d x of the two capillary systems. The permeability is defined as

$$dP_{Pc} = \frac{d\dot{q}}{C_M - C_F}$$

where $d\dot{q}$ is the amount of substance crossing from one capillary to the other per unit time. It should be noted that the placental permeability and the placental diffusing capacity are the same parameter. Diffusing capacity is a term borrowed from respiratory physiology to describe the permeability of a tissue to gases. The diffusion of substances across the placenta would be more properly described in terms of placental permeability, P_P. From the definition of dP_{Pc} we have

$$d\dot{q} = (C_M - C_F)\, dP_{Pc} \quad \text{----------} \quad 6$$

This is equal to the amount of substance taken up in the fetal blood.

$$d\dot{q} = \dot{Q}_{FC}\, d\, C_F \quad \text{----------} \quad 7$$

The same relation holds for the amount lost from the maternal blood.

$$d\dot{q} = -\dot{Q}_{MC}\, d\, C_M \quad \text{----------} \quad 8$$

Combining equations 7 and 8, we have

$$d\dot{q}\left(\frac{1}{\dot{Q}_M} + \frac{1}{\dot{Q}_{FC}}\right) = d(C_F - C_M) \quad \text{-------} \quad 9$$

From equations 6 and 9

$$\left(\frac{1}{\dot{Q}_{MC}} + \frac{1}{\dot{Q}_{FC}}\right) dP_{Pc} = -\frac{d(C_M - C_F)}{(C_M - C_F)} \quad \text{---------} \quad 10$$

Integration of equation 5 yields

$$(C_M - C_F) \left| \frac{(C_{MV} - C_{FV})}{(C_{MA} - C_{FA})} \right. = (1/\dot{Q}_{MC} + 1/\dot{Q}_{FC}) \; P_{Pc} \Big|_{P=0}^{P=P_{Pc}}$$

and

$$\frac{C_{MV} - C_{FV}}{C_{MA} - C_{FA}} = \exp(-P_{Pc}\,(1/\dot{Q}_{MC} + 1/\dot{Q}_{FC})) \text{ ----------11}$$

Equation 11 can be rearranged so that:

$$\frac{C_{MV} - C_{FV}}{C_{MA} - C_{FA}} = \exp\left[-\frac{P_{Pc}}{\dot{Q}_{FC}}\left(1 + \frac{\dot{Q}_{FC}}{\dot{Q}_{MC}}\right)\right] \text{ ----------12}$$

At this stage two dimensionless variables can be defined.

$$d^F = P_P/\dot{Q}_F = P_{PC}/\dot{Q}_{FC} \text{ ----------13}$$

The flow ratio $R^M = \dot{Q}_F/\dot{Q}_M = \dot{Q}_{FC}/\dot{Q}_{MC}$ ---------- 14

The assumptions necessary to these two definitions are that the ratio of capillary permeability to blood flow is constant throughout the placenta and that the fetal to maternal capillary flow ratio is constant throughout the placenta. Equations 13 through 18 illustrate the steps taken by Bartels and Moll (16), Faber and Hart (28) and Faber (27).

Equation 12 becomes

$$\frac{C_{MV} - C_{FV}}{C_{MA} - C_{FA}} = \exp - d^F(1 + R^M) \text{ ----------15}$$

This is not a particularly useful form and it is more convenient to eliminate C_{MV} by using the relationship,

$$\dot{Q}_{MC} (C_{MA} - C_{MV}) = \dot{Q}_{FC} (C_{FV} - C_{FA})$$

so that

$$C_{MV} = C_{MA} - R^{M} (C_{FV} - C_{FA}) \quad \text{----------16}$$

When C_{MV} in equation 15 is replaced by equation 16 and $(C_{MA} - C_{FA}) / (C_{MA} - C_{FA})$ is subtracted from each side of equation 15, we have:

$$\frac{C_{FA} - C_{FV}}{C_{MA} - C_{FA}} = \frac{\exp - d^{F} (1 + R^{M}) - 1}{1 + R}$$

so that the equation for a concurrent placenta is

$$T^{F} = \frac{C_{FV} - C_{FA}}{C_{MA} - C_{FA}} = \frac{1 - \exp - d^{F} (1 + R^{M})}{1 + R} \quad \text{---------- 17}$$

T^{F} is the third dimensionless variable. It should be noted that if a variable T^{M} is defined as $(C_{MA} - C_{MV})/(C_{MA} - C_{FA})$ then $T^{M} = R^{M} T^{F}$. ---------- 18

Considering equation 5, which refers to a concurrent heat exchanger,

$$E = \frac{1 - \exp (- Ntu (1 + C_{min}/C_{max}))}{1 + C_{min}/C_{max}}$$

The analogous relationships depend on the flow ratio R.

Case 1. $\dot{Q}_F < \dot{Q}_M$ $(R < 1)$

$C_{min} = \dot{Q}_F$

$C_{max} = \dot{Q}_M$

tc, out $= C_{FV}$

tc, in $= C_{FA}$

th, out $= C_{MV}$

th, in $= C_{MA}$

The result of these equalities is that, $E = T^F$ and $Ntu = d^F$.

Substituting in equation 5 for $R^M < 1$ we have:

$$T^F = \frac{1 - \exp(1 - d^F(1 + R^M))}{1 + R^M}$$

which is equation 17.

Case 11. $Q_F > Q_M$ $(R^M > 1)$

$E = T^M$

$Ntu = d^M$

$C_{min}/C_{max} = 1/R^M$

so that

$$T^M = \frac{1 - \exp(-d^M(1 + 1/R^M))}{1 + 1/R^M}$$

Substituting $R^M T^F = T^M$ and $R^M d^F = d^M$ we have:

$$T^F = \frac{1 - \exp(-d^F(1 + R^M))}{1 + R^M}$$

which is also equation 17. It follows that solutions to equation 5 are also solutions to equation 17 for all values of $\dot{Q}_M$ and $\dot{Q}_F$.

Solutions to equation 5 and the equations describing other types of exchangers are given by Kays and London (45) in the form of effectiveness - Ntu, relations for C_{min}/C_{max} ratios in the range 0 to 1. The acquisition of solutions to placental equations from these effectiveness - Ntu relations must be made with due regard to the placental flow ratio,

Case 1. $\dot{Q}_F < \dot{Q}_M \quad (R^M < 1)$

Effectiveness $E = T^F$

Capacity rate ratio - $C_{min}/C_{max} = R^M$

Number of transfer units $Ntu = d^F$

Case 11. $\dot{Q}_F > \dot{Q}_M \quad (R^M > 1)$.

$E = RT^F = T^M$

$C_{min}/C_{max} = 1/R^M$

$Ntu = R^M d^F = d^M$

In this way the available solutions for capacity rate ratios in the range 0 to 1 are solutions for placental flows ratio in the range 0 to infinity. Kay's and London's tabular and graphical solutions to the flow patterns of interest are given in tables 2, 3, 4 and 5 and in figures 4, 5, 6 and 7. These solutions are also solutions to equations describing various placental models and may be used as such when the designated substitutions have been made.

Fig. 4. Heat transfer effectiveness as a function of number of transfer units and capacity rate ratio in a concurrent exchanger.

TABLE 2

Concurrent Exchanger Performance

Exchanger effectiveness (E) as a function of capacity-rate ratio (C_{min}/C_{max}) and number of heat transfer units (Ntu)

Ntu	E for indicated capacity-rate ratios, C_{min}/C_{max}				
	0	0.25	0.50	0.75	1.00
0	0	0	0	0	0
0.25	0.221	0.215	0.208	0.202	0.197
0.30	0.393	0.372	0.352	0.333	0.316
0.75	0.528	0.487	0.450	0.418	0.388
1.00	0.632	0.571	0.518	0.472	0.432
1.25	0.713	0.632	0.564	0.507	0.459
1.50	0.777	0.677	0.596	0.530	0.475
1.75	0.826	0.710	0.618	0.544	0.485
2.00	0.865	0.734	0.633	0.554	0.491
2.50	0.918	0.765	0.651	0.564	0.497
3.00	0.950	0.781	0.659	0.568	0.498
3.50	0.970	0.790	0.663	0.570	0.499
4.00	0.982	0.795	0.665	0.571	0.500
4.50	0.989	0.797	0.666	0.571	0.500
5.00	0.993	0.799	0.666	0.571	0.500
∞	1.000	0.800	0.667	0.571	0.500

Reproduced from Kays and London (45)

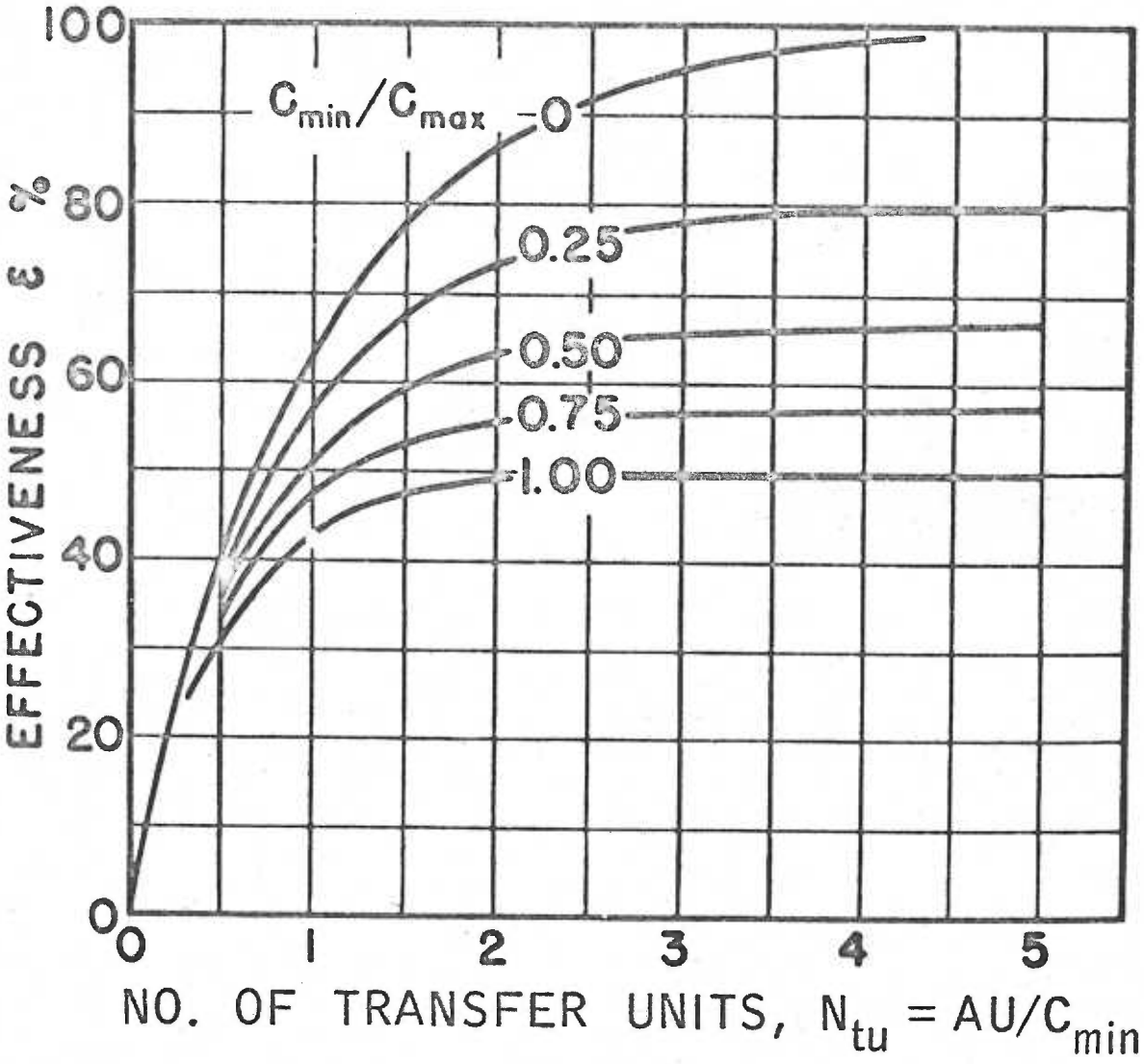

100
80
60
40
20
0
EFFECTIVENESS ε %
C_{min}/C_{max} -0
0.25
0.50
0.75
1.00
0
1
2
3
4
5
NO. OF TRANSFER UNITS, $N_{tu} = AU/C_{min}$

Fig. 5. Heat transfer effectiveness as a function of number of transfer units and capacity rate ratio in a countercurrent exchanger.

TABLE 3

Countercurrent Exchanger Performance (45)

Exchanger effectiveness (E) as a function of capacity-rate ratio (C_{min}/C_{max}) and number of heat transfer units (Ntu)

Ntu	E for indicated capacity-rate ratios, C_{min}/C_{max}							
	0	0.25	0.50	0.70	0.75	0.80	0.90	1.00
0	0	0	0	0	0	0	0	0
0.25	0.221	0.216	0.210	0.206	0.205	0.204	0.202	0.200
0.50	0.393	0.378	0.362	0.350	0.348	0.345	0.339	0.333
0.75	0.528	0.502	0.477	0.457	0.452	0.447	0.438	0.429
1.00	0.632	0.598	0.565	0.538	0.532	0.525	0.513	0.500
1.25	0.713	0.675	0.635	0.603	0.595	0.587	0.571	0.556
1.50	0.777	0.735	0.691	0.655	0.645	0.636	0.618	0.600
1.75	0.826	0.784	0.737	0.697	0.687	0.677	0.657	0.636
2.00	0.865	0.823	0.775	0.733	0.722	0.711	0.689	0.667
2.50	0.918	0.880	0.833	0.788	0.777	0.764	0.740	0.714
3.00	0.950	0.919	0.875	0.829	0.817	0.804	0.778	0.750
3.50	0.970	0.945	0.905	0.861	0.848	0.835	0.807	0.778
4.00	0.932	0.962	0.928	0.836	0.873	0.860	0.831	0.800
4.50	0.989	0.974	0.944	0.905	0.893	0.880	0.850	0.818
5.00	0.993	0.982	0.957	0.921	0.909	0.896	0.866	0.833
5.50	0.996	0.998	0.968	0.933	0.922	0.909	0.880	0.846
6.00			0.975	0.944		0.921	0.892	0.857
6.50			0.980	0.953		0.930	0.902	0.867
7.00			0.985	0.960		0.939	0.910	0.875
7.50			0.988	0.966		0.946	0.918	0.882
8.00			0.991	0.971		0.909	0.880	0.846
8.50			0.993	0.975		0.957	0.931	0.895
9.00			0.994	0.979		0.962	0.936	0.900
9.50			0.996	0.982		0.966	0.941	0.905
10.00			0.997	0.985		0.970	0.945	0.909
∞	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

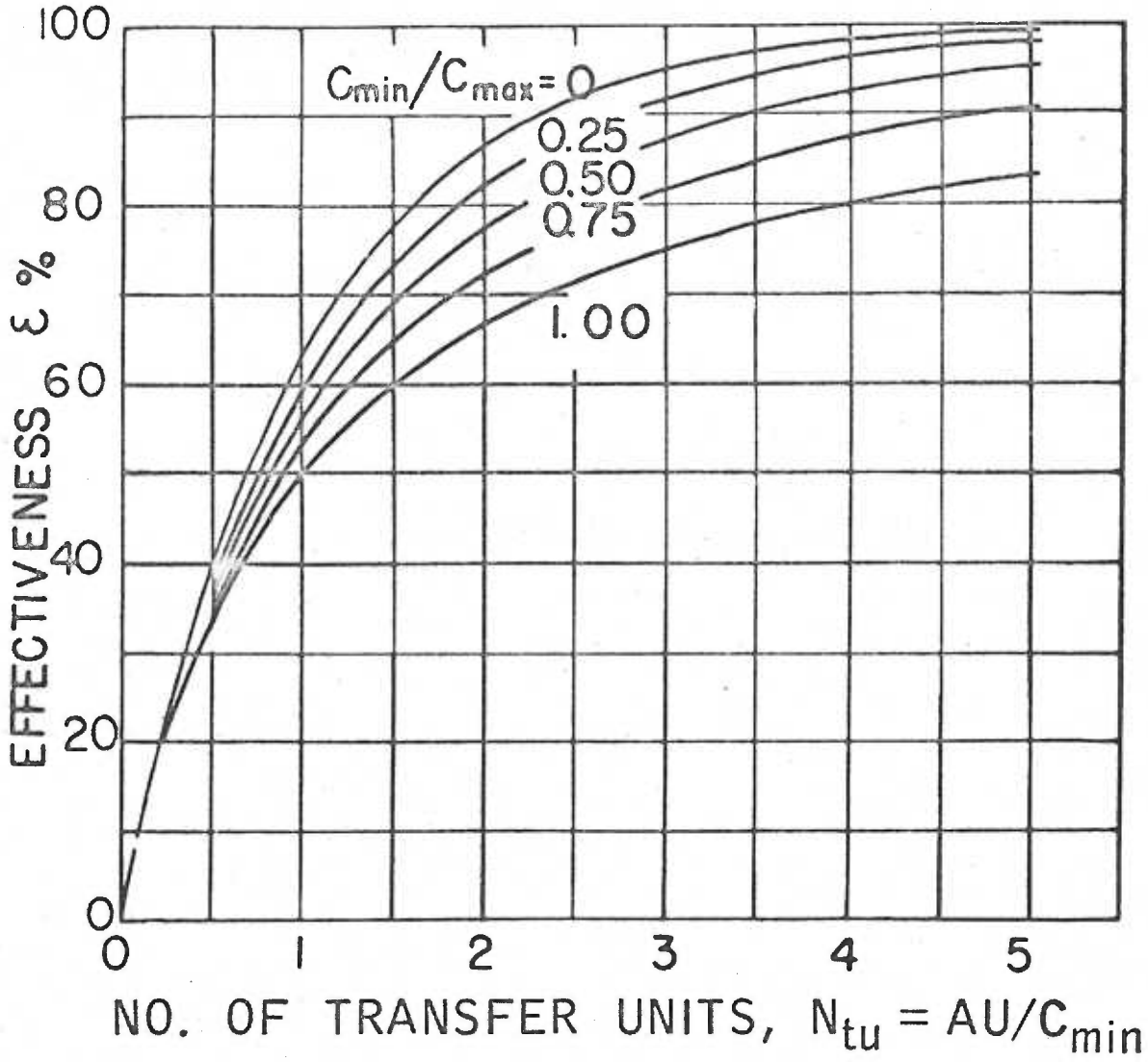

100
80
60
40
20
0
EFFECTIVENESS ε %
C_{min}/C_{max} = 0
0.25
0.50
0.75
1.00
0
1
2
3
4
5
NO. OF TRANSFER UNITS, $N_{tu} = AU/C_{min}$

Fig. 6. Heat Transfer effectiveness as function of number of transfer units and capacity rate ratio in a cross current exchanger with fluids unmixed.

TABLE 4

Crosscurrent Exchanger with Both Fluids Unmixed

Crossflow (both fluids unmixed) exchanger effectiveness (E) as a function of capacity-rate ratio (C_{min}/C_{max}) and number of heat transfer units (Ntu)

Ntu	E for indicated capacity-rate ratios, C_{min}/C_{max}				
	0.00	0.25	0.50	0.75	1.00
0.00	0.000	0.000	0.000	0.000	0.000
0.25	0.221	0.215	0.209	0.204	0.199
0.50	0.393	0.375	0.358	0.341	0.326
0.75	0.528	0.495	0.466	0.439	0.413
1.00	0.632	0.588	0.547	0.510	0.476
1.25	0.714	0.660	0.610	0.565	0.523
1.50	0.777	0.716	0.660	0.608	0.560
1.75	0.826	0.761	0.700	0.642	0.590
2.00	0.865	0.797	0.732	0.671	0.614
2.50	0.918	0.851	0.783	0.716	0.652
3.00	0.950	0.838	0.819	0.749	0.681
3.50	0.970	0.915	0.848	0.776	0.704
4.00	0.982	0.934	0.869	0.797	0.722
4.50	0.989	0.948	0.887	0.814	0.737
5.00	0.993	0.959	0.901	0.829	0.751
6.00	0.997	0.974	0.924	0.853	0.772
7.00	0.999	0.983	0.940	0.871	0.789
∞	1.000	1.000	1.000	1.000	1.000

Reproduced from Kays and London (45).

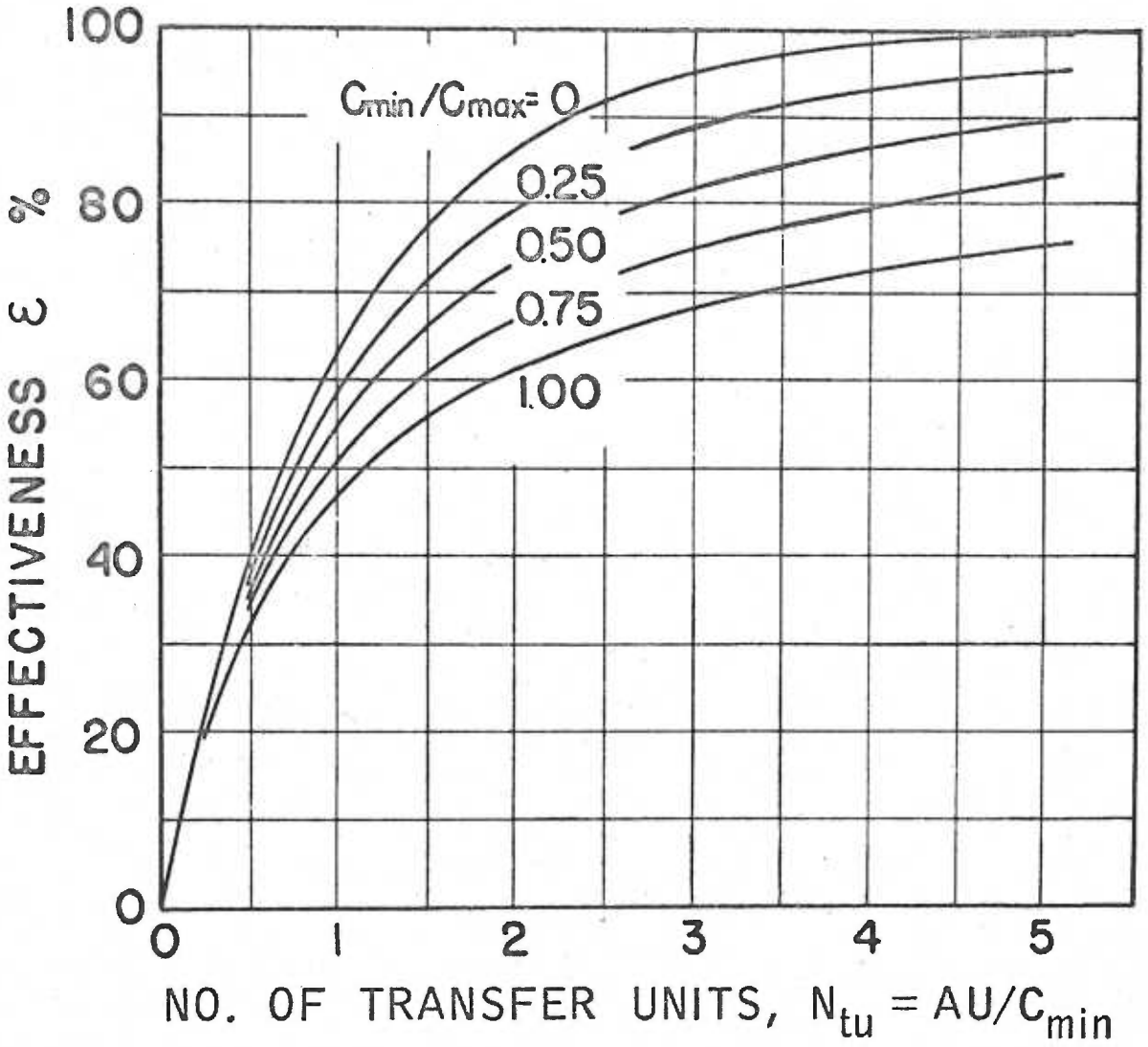

100
80
60
40
20
0
EFFECTIVENESS ε %
Cmin/Cmax= 0
0.25
0.50
0.75
1.00
0
1
2
3
4
5
NO. OF TRANSFER UNITS, Ntu = AU/Cmin

Fig. 7. Heat transfer effectiveness as a function of number of transfer units and capacity rate ratio in a crosscurrent exchanger with one fluid mixed.

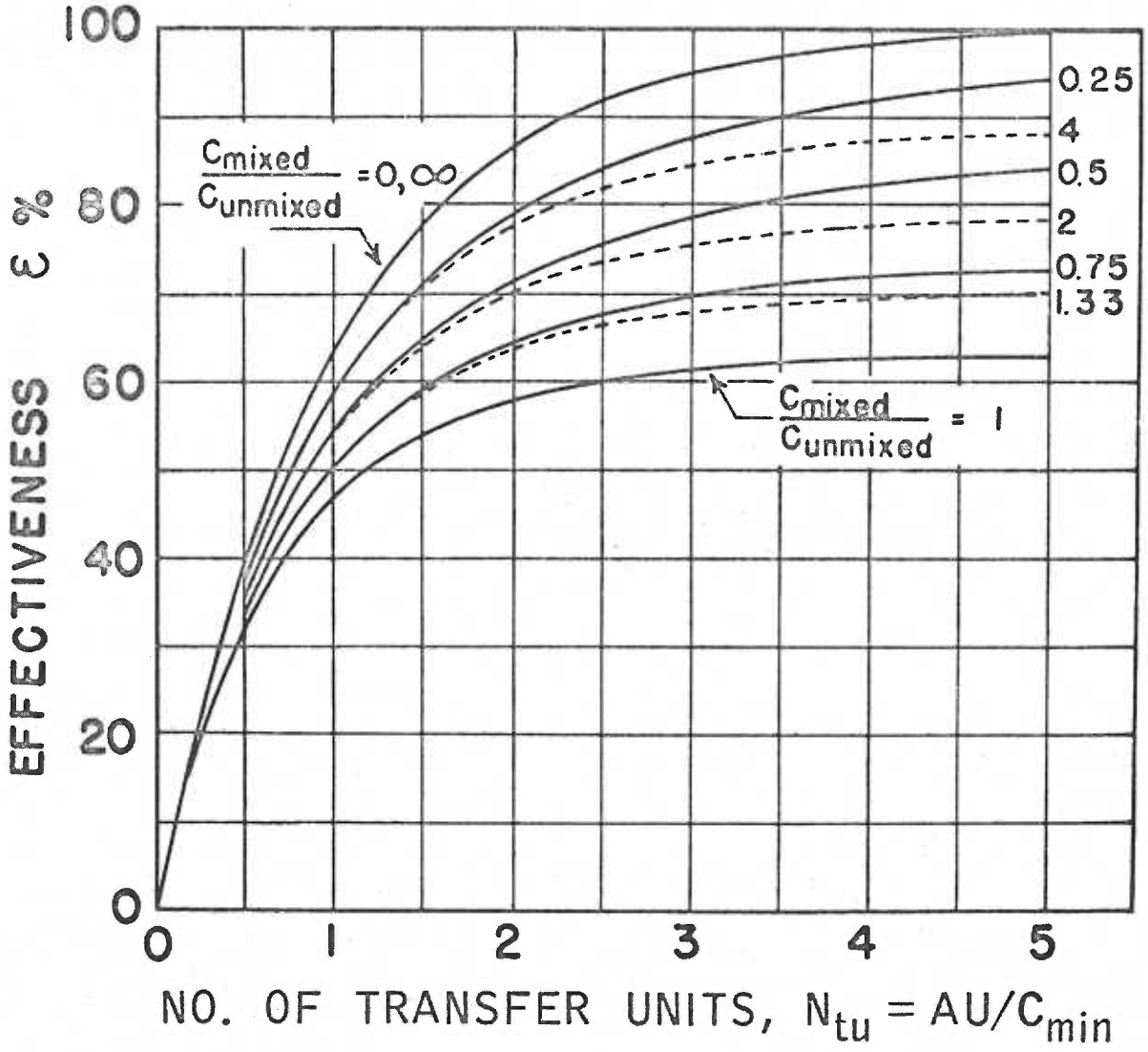
TABLE 5

Crosscurrent Exchanger with One Fluid Mixed

Crosscurrent (one fluid "mixed", the other fluid"unmixed") exchanger effectiveness (E) as a function of capacity-rate ratio ($C_{mixed}/C_{unmixed}$) and number of heat transfer units (Ntu)

Ntu	E for indicated capacity-rate ratios, $C_{mixed}/C_{unmixed}$							
	0	0.25	4.00	0.50	2.00	0.75	1.333	1.000
0	0	0	0	0	0	0	0	0
0.25	0.221	0.215	0.213	0.209	0.209	0.204	0.204	0.198
0.50	0.393	0.375	0.375	0.358	0.357	0.341	0.341	0.325
0.75	0.528	0.495	0.494	0.465	0.463	0.463	0.435	0.410
1.00	0.632	0.587	0.585	0.545	0.542	0.505	0.503	0.469
1.25	0.713	0.658	0.654	0.605	0.600	0.556	0.552	0.510
1.50	0.777	0.714	0.706	0.652	0.644	0.594	0.589	0.540
1.75	0.826	0.758	0.747	0.689	0.677	0.623	0.616	0.562
2.00	0.865	0.793	0.778	0.715	0.702	0.645	0.636	0.579
2.50	0.918	0.844	0.820	0.760	0.736	0.677	0.663	0.601
3.00	0.950	0.879	0.846	0.789	0.756	0.697	0.679	0.613
3.50	0.970	0.903	0.861	0.808	0.768	0.710	0.689	0.621
4.00	0.982	0.920	0.870	0.823	0.776	0.718	0.695	0.625
4.50	0.989	0.933	0.876	0.834	0.780	0.724	0.698	0.628
5.00	0.993	0.942	0.880	0.841	0.783	0.728	0.700	0.630
	1.000	1.000	0.885	0.865	0.787	0.736	0.703	0.632

Reproduced from Kays and London (45)


100
80
60
40
20
0
EFFECTIVENESS ε %
0
1
2
3
4
5
NO. OF TRANSFER UNITS, $N_{tu} = AU/C_{min}$
$\frac{C_{mixed}}{C_{unmixed}} = 0, \infty$
$\frac{C_{mixed}}{C_{unmixed}} = 1$
0.25
4
0.5
2
0.75
1.33

MODERN TECHNIQUES OF FUNCTIONAL ANALYSIS

In the preceding section, it was shown that the theoretical approach used by engineers to predict the behavior of heat exchangers may be applied to models of the placenta. The engineer would use these techniques to design a heat exchanger to function at a particular set of effectiveness - Ntu relations. A physiologist would be more interested in observing the effectiveness - Ntu relations of a placenta and predicting the placental models capable of generating the observed relations. The tables of various effectiveness - Ntu relations in the literature should be equally useful in each of these applications.

In an earlier section the deviation of real placentas from model placentas was discussed. It was shown that the mammalian placenta is a complicated organ that cannot be represented by a simple model. This section will discuss the application of various theoretical procedures to the analysis of placental function to see whether or not the theory which applies to simple models can be changed to describe the more complex models which are more representative of the physiological organ.

Three different procedures are currently available for the analysis of placental function. The graphical analysis of respiratory gas transfer in the primate placenta of Ross (74), the clearance analysis of Meschia et al. (54) and the application of effectiveness

- Ntu relation theory which has been initially described by Bartels and Moll (16) and later improved by Faber and Hart (28) and Faber (27).

In 1967 Ross (74) used the fact that the ratio of the change in carbon dioxide to that of oxygen (R*) must be the same on both sides of the exchanging area provided that all of the change is due to transplacental exchange and none due to tissue metabolism. The maternal and fetal R* lines were constructed graphically using P_{CO_2} as the abcissa and P_{O_2} as the ordinate. The application was designed specifically for the primate placenta where Ross considers it to be a useful source of information as to the physiological significance of intervillous blood. It is hardly applicable to non-primate placentas which do not have an anatomical equivalent of the intervillous space. As has been stated earlier it is improbable that an analytical approach, that assumes that there is no consumption of oxygen by the uteroplacental tissue will be of much practical value in the study of the cotyledonary placenta.

At about the same time Meschia, Battaglia, and Bruns (54) had been observing the movement of antipyrene across the sheep placenta. They could only infuse the antipyrene into one fetus even if there were twins present. In this situation the concentration of antipyrene in the uterine venous sample is of questionable value. The uterine venous blood can be sampled from the left or right

common uterine vein. Unless the infused placenta is all on one side or evenly distributed throughout the whole uterus then the uterine venous sample from one common uterine vein will have a concentration of antipyrene less than if the placenta was all on that side and greater than if the placenta were evenly distributed throughout the uterus. Meschia et al. also found that they could sample fetal arterial blood from the fetal femoral artery but that umbilical venous blood had to be obtained from the cord. They found that any manipulation of the cord resulted in vaso-constriction and a concommitant decrease in umbilical blood flow.

The aim of this group was to devise a form of data analysis that did not require the use of any venous samples. They knew the rate of antipyrene infusion $\dot{q}$, the maternal $(MA)_A$ and fetal $(FA)_A$ arterial antipyrene concentrations. They defined the diffusion clearance of antipyrene C^*_A as: $C^*_A = \dot{q} / ((FA)_A - (MA)_A)$. The equations for countercurrent and concurrent exchangers were derived and a table of predicted clearances in these exchangers under various conditions was presented. The authors' primary interest lay with the degree of diffusion limitation (L_D), a concept developed by Piiper et al. (69). The degree of diffusion limitation is defined as the relative decrease of clearance predicted to occur when the placental diffusing capacity is decreased from infinity to the actual value.

$$L_D = (C^*_{max} - C^*) / C^*_{max}$$

where C^*_{max} represents the clearance of an infinitely diffusible substance. This approach of Meschia et al. should be very valuable in the study of placental diffusion limitation and the permeability of the placenta to a variety of substances. It will also be useful when the venous samples are difficult to get or of doubtful value. The predicted model analysis is very clumsy when compared to the effectiveness - Ntu relation technique. It is probable that attempts to determine the vascular arrangement of the placenta would be more profitably based on effectiveness - Ntu relations.

The first application of effectiveness - Ntu relations to the placenta was described by Bartels and Moll in 1964 (16). They were especially interested in the human placenta and derived an equation that described the human placenta as a multivillous stream system. The architecture of the human placenta is not within the scope of this discussion. The relevant aspects of this work are the use of effectiveness - Ntu relations to describe the transfer of inert substances and oxygen across the placenta.

Bartels and Moll (16) realized that the use of C_{min} and C_{max} in the effectiveness - Ntu relations was inadequate when these relations were applied to the placenta. In a heat exchanger it may be of little consequence which flow is the larger but in a placenta the fetal placental flow must always be distinguished from the

maternal placental flow. The capacity rate ratio used in the effectiveness - Ntu relations was defined as the lesser fluid capacity rate divided by the larger fluid capacity rate. Placental analogs will require that the flow ratio be defined as the maternal blood capacity divided by the fetal blood capacity or vice versa.

Bartels and Moll described the placental transfer of an inert substance, equally soluble in maternal and fetal blood, by plotting an effectiveness - Ntu diagram where effectiveness was defined as: $C_{FV} - C_{FA} / C_{MA} - C_{FA}$ which is the quantity referred to as T^F in the preceding section. The number of transfer units Ntu was defined as the placental permeability (P_P) divided by the fetal blood flow rate ($\dot{Q}_F$). This type of plot can only be compared to the effectiveness - Ntu plot when the ratio of fetal to maternal flow is less than one. Bartels and Moss defined their flow ratio R^F as maternal placental flow divided by fetal placental flow $\dot{Q}_M/\dot{Q}_F$ which is always greater than 1 when $\dot{Q}_F$ is the lesser flow. The $T^F d^F$ relationships for several types of exchangers can be obtained from the tables given in the preceding section in the following way:

T^F = Effectiveness (E)

d^F = Number of transfer units (Ntu)

R^F = The reciprocal of the capacity rate ratio $1/(C_{min}/C_{max})$

The tables contain C_{min}/C_{max} values in the range 0 to 1 so that the substitutions described above generate R^F lines in the range 1 to infinity. Bartels and Moll show a R^F value of 0·5 on the same graph, a representation analagous to that used by Hausen (38). This is somewhat difficult to interpret in terms of the effectiveness - Ntu relations technique because when the flow ratio is less than 1, the effectiveness becomes T^M instead of T^F and the abcissa becomes d^M instead of d^F. The $T^F d^F$ plot can only be made for R^F values of less than 1 by making a different set of substitutions. These substitutions are:

T^F = Effectiveness times capacity rate ratio.

$E(C_{min}/C_{max})$

d^F = Number of transport units times capacity rate ratio.

$Ntu(C_{min}/C_{max})$

R^F = Capacity rate ratio. (C_{min}/C_{max}).

When these precautions are taken, T^F can be plotted against d^F for all values of R^F from the tables of effectiveness - Ntu relations.

Bartels and Moll (16) discuss the means whereby placental oxygen transfer can be described by these techniques. Oxygen is not present in blood in physical solution only, but as physically dissolved oxygen and as hemoglobin bound oxygen. The authors pointed

out that if the oxygen disassociation curve were a straight line, then the equations describing the transplacental diffusion of substances in physical solution can be modified to apply to oxygen transfer by replacing $\dot{Q}_M$ and $\dot{Q}_F$ with $a_M\dot{Q}_M$ and $a_F\dot{Q}_F$, where a_M and a_F are the effective solubilities of oxygen in maternal and fetal blood. The effective solubility is defined by the relationship

$$a = d\ C_{tot}/d\ P_{O_2}$$

where C_{tot} is the total change in oxygen concentration in the blood and $d\ P_{O_2}$ is the change in oxygen partial pressure in the blood.

The relation between oxygen content and partial pressure is not a straight line in blood but Bartels and Moll (16) state that during maternal hypoxia it is a good approximation. Under normal circumstances the authors do not think this approach is valid and show that the application of Lamport's modification of the Bohr integral (50) can be used to construct a T^F, d^F plot for oxygen transfer similar to that for the transfer of inert substances. These methods assume that there are no shunts and that there is no uteroplacental oxygen consumption. These two assumptions are invalid and the technique, though interesting, is unlikely to be directly useful.

Bartels and Moll made no attempt to apply this analytical procedure to any experimental preparation, nor did they use it to evaluate any of the data in the existing literature. They did not

consider the possible effects of uneven distributions of flow and permeability. Their main object was to present a theoretical discussion of oxygen transfer in the human placenta. This is one of the more sophisticated considerations in the field of placental physiology that is unlikely to be adequately defined until the placental transfer of inert molecules is more fully understood, in preparations more accessible to experimental observations, than the human placenta.

The application of this type of analysis to an experimental preparation was first accomplished by Faber and Hart in 1966 (28). They used an analytical procedure based on effectiveness - Ntu relations to evaluate data obtained from the perfused rabbit placenta. The authors' description of the analysis is somewhat difficult to comprehend for two reasons. Firstly, the relationship between the dimensionless parameters used in this study and the analagous parameters used in effectiveness - Ntu relations is not described. For this reason the numerical solutions to equations representing the behavior of various model exchangers cannot be easily used. In fact, Faber and Hart solved the various equations without recourse to the available numerical solutions even though these solutions could have been applied directly. The second source of difficulty is that the authors introduce the theory of the analysis by referring the reader to the work of Bowman et al. (19)

and Bartels and Moll (16). Bowman et al. based their approach to heat exchange on "log-mean rate equations" whereas Bartels and Moll used an approach based on effectiveness - Ntu relations. These are two very different analytical methods and the one to one correspondence between them is not obvious. Kays and London (45) prove this relationship and compare the two methods. They give several examples and show that the effectiveness - Ntu approach is simpler and more straight forward than the "log-mean temperature difference" approach which involves successive approximations. They further pointed out that the effectiveness - Ntu approach is based on dimensional parameters that are more easily visualized than the parameters employed in the "log-mean temperature difference" approach. Faber and Hart use an analysis which is based on effectiveness - Ntu relations making it difficult to correlate the work of Bowman et al. with the ensuing discussion. Discussion of effectiveness - Ntu relations can be found in several basic texts concerned with heat transfer (33, 44, 74) and in the preceding section.

When they considered substances that are present in physical solution only, Faber and Hart defined the following three dimensionless variables: $T = C_{MA} - C_{MV} / C_{MA} - C_{FA}$, $R = \dot{Q}_F / \dot{Q}_M$, $d = P_P / \dot{Q}_M$ where P_P is the permeability of the placenta. These variables can be written in the nomenclature pre-

viously used in this discussion as T^M, R^M and d^M. For purposes of comparison Bartels and Moll used the variables T^F, R^F and d^F where $T^F = C_{FV} - C_{FA}/C_{MA} - C_{FA}$, $R^F = \dot{Q}_M / \dot{Q}_F$, $d^F = P_P/\dot{Q}_F$. It is apparent that these two sets of variables can be equated in the following way:

Faber and Hart	Bartels and Moll	Relationship
$T^M = \frac{C_{MA} - C_{MV}}{C_{MA} - C_{FV}}$	$T^F = \frac{C_{FV} - C_{FA}}{C_{MA} - C_{FA}}$	$T^M = T^F/R^F$
$R^M = \dot{Q}_F/\dot{Q}_M$	$R^F = \dot{Q}_M/\dot{Q}_F$	$R^M = 1/R^F$
$d^M = P_P/\dot{Q}_M$	$d^F = P_P/\dot{Q}_F$	$d^M = d^F/R^F$

It has been shown that values for the variables used by Bartels and Moll can be taken from the tables and figures, defining the effectiveness - Ntu relations for various exchangers, given in the preceding section. The relationship between the variables used by Bartels and Moll (16) and those used by Faber and Hart show that the variables used by the latter can be similarly evaluated. The procedure is as follows:

Case 1. $\dot{Q}_F < \dot{Q}_M$ $(R^M < 1)$

T^M = Effectiveness (E) divided by the Capacity rate ratio (C_{min}/C_{max}).

d^M = Capacity rate ratio (C_{min}/C_{max}) times

the number of transfer units (Ntu).

R^M = Capacity rate ratio (C_{min}/C_{max}).

Case 11. $Q_F > Q_M$ ($R^M > 1$)

T^M = Effectiveness (E).

R^M = The reciprocal of the capacity rate ratio.

d^M = Number of transport units (Ntu).

In this way solutions to the equations relating the variables T^M, R^M and d^M can be rapidly obtained for many types of exchangers from the published tables.

Faber and Hart pointed out that in experimental situations the value of d^M is usually not known whereas T^M and R^M can be measured relatively easily. For this reason they plotted T^M as the ordinate and R^M as the abcissa. This is equivalent to a relation between effectiveness and capacity rate ratio.

Faber and Hart were primarily concerned with the application of this analysis to oxygen transfer as were Bartels and Moll. The fact that oxygen is not present in blood in physical solution only, was recognized by redefining the dimensionless variables as follows:

$$T^M_{O_2} = \frac{(Sat^{MA} - Sat^{MV})\ (O_2)^M_{1/2}}{Sat^{MA}(O_2)^M_{1/2} - Sat^{FA}(O_2)^F_{1/2}}$$

where the superscripts M, F, A and V denote maternal, fetal, arterial and venous respectively. The notation Sat means fractional satura-

tion of the hemoglobin. The notation $(O_2)_{1/2}$ denotes the concentration of oxygen in physical solution at which 50% of the hemoglobin is saturated with oxygen.

$$R^M = f^F \dot{Q}_F / f^M \dot{Q}_M \quad \text{and} \quad d^M = P / f^M \dot{Q}_M$$

where f is the ratio of the amount of oxygen in the blood to $(O_2)_{1/2}$.

The authors perfused the placentas of 30 rabbits at a gestational age of 27 to 29 days. They could not obtain uterine venous samples but assumed that the rabbit placenta functioned as a countercurrent exchanger. In this type of exchanger the uterine venous P_{O_2} would be equal to zero, (the fetal arterial P_{O_2}), if oxygen equilibrated across the exchanging capillaries. Evidence that this did occur was provided by comparing the fetal to maternal acetylene transfer to the maternal to fetal oxygen transfer. These two rates of transfer were sufficiently close for the authors to conclude that oxygen does equilibrate across the exchanging capillaries of the rabbit placenta.

The placental oxygen consumption was measured by occluding the maternal uterine flow and observing the rate of oxygen removal from the placental circuit. The value for $\dot{Q}_M$ was multiplied by (1 - the amount of oxygen consumed by the placenta divided by the amount of oxygen delivered to the placenta). This procedure removed the fraction of the uterine blood flow that was delivering

oxygen to the placental tissues rather than to the fetal circulation.

The T^M, R^M plot for oxygen transfer as experimentally observed in the rabbit placenta was illustrated. This constituted the first application of the effectiveness - Ntu approach to data obtained from a placenta. The value of the experiment was limited by the lack of maternal venous samples but the usefulness of the approach is clearly apparent. Once again it should be stated that the approach would be more usefully applied to the placental transfer of inert molecules or at least molecules that are only present in physical solution. Faber and Hart discuss the possible errors involved in comparing a placenta to a simple exchanger but do not describe a means of compensating for them.

A theoretical approach to the problem was described by Faber (27) in a recent abstract. In this work Faber plots T^M against T^F and uses d^M as the third variable. The usefulness of this plot is not immediately apparent because when the flows are not differentiated the representation is symmetrical as applied to a simple model. The ordinate and abscissa being respectively equal to E divided by C_{min}/C_{max} and E, when R^M is less than 1 and E and E divided by C_{min}/C_{max}, when R^M is greater than 1. The placenta, however, is not a simple model. Some blood is shunted on each side of the placenta. It has been shown that

that

$$\lim_{R^M \to O} \frac{C_{FV} - C_{FA}}{C_{MA} - C_{FA}} = 1 - S_F$$

where S_F, the fetal shunt, is the fraction of the umbilical flow that does not reach the exchanging area. By a similar argument it can be shown that

$$\lim_{R^M \to O} \frac{C_{MA} - C_{MV}}{C_{MA} - C_{FA}} = 1 - S_M$$

where S_M, the maternal shunt, is the fraction of the uterine blood flow that does not participate in exchange.

The relation $T^M = R^M T^F$ shows that when $R^M = O$, T^M is O and the exchanger is operating at a point on the T^F axis. In a simple model this is at the point $T^F = 1$ but when there is a fetal shunt the $R^M = O$ point is at $T^F = 1 - S_F$. Similarly, when R^M is infinity, $T^F = O$, and the exchanger is operating at a point on the T^M axis. When a maternal shunt exists, $T^M = 1 - S_M$ when R^M = infinity. It follows from these arguments that if an experiment can be devised which will produce values for T^M and T^F, these values when plotted on a $T^M T^F$ diagram will produce a line which will have an intercept on the T^M and T^F axes. These intercepts will then provide values for the maternal and fetal placental shunts. This information can also be obtained from T^M R^M and T^F R^M plots but two separate representations would be required. Faber

showed that in the presence of shunts the $T^M T^F$ line representing a model exchanger with no shunts would represent the behavior of the same model with shunts if all T^M values were multiplied by $1 - S_M$ and all T^F values were multiplied by $1 - S_F$.

Faber (27) also investigated the consequences of uneven distribution of permeability and flow ratio over the placental area. He divided a hypothetical placenta into 5 compartments and distributed the permeability and flow ratios unevenly among the compartments. A digital computer was programmed to calculate the effect of the uneven distribution on the venous concentrations of an exchanging substance and the consequent values of T^M and T^F. Faber found that the uneven distribution of permeability did not grossly affect the $T^M T^F$ plot but that the uneven distribution of flow ratios caused gross changes.

In this section we have described the various modern techniques that can be applied to the analysis of placental function. The application of approaches based on effectiveness - Ntu relations to placental exchange appears to be potentially useful, especially as applied to the transfer of molecules that are present in physical solution only. The relatively slow acceptance of these techniques may stem from the desire for workers in the field to examine the transplacental movement of oxygen and the specific difficulties inherent in this particular problem. The modifications of the

effectiveness - Ntu approach by Bartels and Moll (16), Faber and Hart (28) and Faber (27) have produced an analytical technique whereby placental exchange can be examined with a meaningful appreciation of the fact that the placenta is not a simple exchanger.

SUMMARY OF INTRODUCTION

In the preceding discussion, the literature pertaining to the mammalian placenta as an organ of exchange has been reviewed. There are two distinct ways to describe an exchanger. It can be taken apart and examined, the various components can be measured and described and the performance of the exchanger predicted from this information. If this approach cannot be implemented, either because the exchanger cannot be taken apart, or because the necessary measurements cannot be made, then the exchanger can be tested under controlled conditions. In this case an understanding of the system is obtained from the knowledge of what it does rather than what it is. The question asked in each case is: what is it and what does it do? The knowledge of what it is can be obtained from what it does and the knowledge of what it does can be obtained from what it is. The first 4 sections of this introduction were largely concerned with attempts to describe what the placenta is.

Many years of anatomical research have produced little information that is of physiological value. The rabbit placenta is

very probably a countercurrent exchanger (63) but the sheep or goat placenta appears to be too complex a system to be defined by anatomical studies. The early work of Barcroft and Barron (8), which seemed to prove that the sheep placenta was a countercurrent exchanger, has been vigorously debated by several workers (59, 77, 78, 83, 84). This type of placenta seems to be neither a countercurrent nor a concurrent exchanger. The most recent evidence (59, 78) leads to the conclusion that the exchanging vessels of the sheep placenta are arranged in an essentially undefineable manner, which may bear some resemblance to a crosscurrent exchanger. Histological studies have not been of much help in the definition of the permeability of the inter-capillary tissue. The thickness of this tissue layer seems to vary over the surface of the placenta (84), and the resistance that this layer imposes to diffusion does not seem to be uniform across the thickness of the layer (55).

Information gained from the observation of placental hemodynamics has been relatively more useful but essential facts are still lacking. Umbilical and uterine pressures and flows have been measured (48, 57) but the fraction of these flows that actually participates in transplacental exchange is largely undefined. Measurements of placental intravascular volume have not been broken down into arterial, capillary and venous components so that the essential information, the amount of blood in the exchanging cap-

illaries, is not available.

The placental diffusing capacity is a function of the area, thickness and diffusion coefficient of the exchanging surfaces. Most measurements of this quantity have concerned oxygen (11, 12, 30) and assumptions necessary to this application have been shown to be largely invalid.

The studies of placental function that attempt to describe what the placenta does rather than what it is are described in the last two sections. This approach has been developed relatively recently. The early application of analyses based on the theory of heat exchangers has concerned the placental transfer of oxygen (16, 28). These studies have been discussed and it was shown that although an approach based on the theory of heat exchangers should be very useful in the description of respiratory gas transfer, it is best suited to the examination of the transplacental exchange of non-metabolites.

The exchanging characteristics of the cotyledonary placenta have not been adequately defined. Theoretically, it is possible to describe this type of placenta by constructing a $T^{M}_{T^{F}}$ plot of the type described by Faber (27). This could be done by observing the uterine and umbilical, arterial and venous concentrations of an inert tracer substance over a wide range of flow ratios. Such a graph would not be particularly useful unless a value could be

assigned to the dimensionless variable d^M. This would involve measuring the diffusing capacity of the placenta for the tracer in question, a procedure which has not been very successful in the past. This problem could be overcome by using a very diffusible tracer. The data illustrated in figures 4, 5, 6, and 7 shows that the effectiveness of all the models changes very little in the range of Ntu values between 10 and infinity. This means that as long as d^M is greater than 10 then the transplacental exchange of the tracer would be indistinguishable from that of an infinitely diffusible substance and d^M need not be measured. If such a plot could be compared to the predicted behavior of various models with various degrees of shunting and uneven distributions of flow, these comparisons would permit conclusions to be drawn as to the architecture of the exchanging capillaries, the evenness with which the flows are distributed over the exchanging area and the amount of shunting that is present. The following conditions must be satisfied by the design of such an experiment.

1. The tracer used must be sufficiently diffusible that its rate of transplacental diffusion is indistinguishable from that of an infinitely diffusible substance. In the nomenclature of Meschia et al. (54) the degree of diffusion limitation L_D should be close to zero. It must be inert, normally absent from the uterine and umbilical circulations and equally soluble and present in solution only in the

maternal and fetal blood.

2. There must be a rapid accurate reliable method to measure the concentration of tracer substance in a blood sample.

3. There must be a method whereby the umbilical and uterine blood flows can be measured.

4. The preparation must provide access to representative samples of blood flowing in the umbilical and uterine arteries and veins.

5. The ratio of these flows must be under control such that it can be varied from 0 to infinity.

6. There must be some means of knowing whether or not the samples were drawn when the transplacental exchange of the tracer was in a condition of equilibration and not under the influence of transient changes.

The succeeding chapters of this thesis describe an experiment wherein these conditions were satisfied and a $T^{M}{}_{T}{}^{F}$ plot of the goat placenta was obtained. This graph is compared to the predicted behavior of several placental models and conclusions are drawn as to the physical characteristics of the goat placenta.

MATERIALS AND METHODS

The introductory chapter provided a survey of the literature pertaining to the exchanging characteristics of the sheep and goat placenta. It was shown that techniques are available whereby it may be possible to describe some of the hitherto undefined characteristics of such a placenta provided that certain conditions are met in the design of the experiment.

The techniques that were employed to satisfy these conditions will be described in detail. A preliminary section is presented to outline the relevance of each detail to the whole fabric of the experimental design. Here, the techniques employed to meet the specified conditions will be briefly described and a short statement of the procedure will be presented. Subsequent sections will describe in detail the surgical preparation, the mechanical devices that subserve the surgical preparation and the chemical analyses that were applied.

A. PERSPECTIVES

In the summary of the introduction several conditions were specified which must be satisfied by the experimental design. The means whereby these conditions were satisfied were as follows:

1. The inert gases, nitrous oxide (N_2O) and acetylene (C_2H_2) were both considered to be suitable for use as tracer sub-

stances.

2. There had to be a method whereby the umbilical and uterine blood flows could be measured. This condition was met in conjunction with a further problem posed by the use of an inert tracer such as N_2O or C_2H_2. If N_2O were introduced on the maternal side it would pass across the placenta and accumulate in the fetal side. This process would continue until the concentration of N_2O in the fetal tissue was the same as that in the maternal artery. In this situation there would be no net flux of N_2O across the placenta. To avoid this, the fetus was replaced by a pump and blood pumped into the umbilical arteries. The umbilical venous outflow was passed through an exchanger and recirculated through the placenta. This procedure provided both a means of removing the N_2O from the fetal placental circulation and a means of measuring the uterine and umbilical blood flows. The maternal flow was measured by using the fact that the amount of gas lost from one of the flows is equal to the amount of gas gained by the other flow, i.e.

$$\dot{Q}_M (C_{MA} - C_{MV}) = \dot{Q}_F (C_{FV} - C_{FA})$$

where C is the concentration of N_2O in each of the vessels. As $\dot{Q}_F$ was the predetermined output of a pump and C_{MA}, C_{MV}, C_{FV} and C_{FA} could all be measured, the only unknown is $\dot{Q}_M$ which could be calculated.

3. The preparation had to provide access to the relevant

blood vessels. The umbilical arterial and venous bloods were sampled by tapping onto the pumping circuit at appropriate places and the maternal arterial blood was sampled via a carotid catheter. The uterine venous blood was sampled by putting catheters into a superficial uterine vein on the left and right sides of the uterus and advancing them until the tips were in the common uterine veins on each side. Twin pregnancies were used because the two placentas are usually on different sides of the bicornate uterus. Each uterine venous catheter would then sample representative blood serving the fetus on that side.

4. The ratio of the fetal blood flow to the maternal blood flow had to be under control and capable of being varied from zero to infinity. This was done by varying the rate of the pump and by partially constricting the maternal abdominal aorta. The amount of constriction was judged by comparing the femoral and carotid arterial pressures. It was anticipated that very high and very low flow ratios would be difficult to obtain by this technique. For this reason the carbon monoxide (CO) technique of Metcalfe et al. (59) was applied to the placenta and uterus. Proof that this procedure would produce apparent flow ratios of zero and infinity respectively by virtue of the hemoglobin on one side of the placenta taking up all of the CO from the other side without increasing the P_{CO} of the blood, is presented in a later chapter.

5. Transient, time dependent, variations in the venous concentrations of N_2O or C_2H_2 had to be avoided. This was done by adding N_2O to the maternal breathing mixture and C_2H_2 to the gas flowing through the exchanger in the fetal circuit. This resulted in the transfer of C_2H_2 from the fetal to the maternal side of the placenta and N_2O from the maternal to the fetal side of the placenta. Proof is submitted in a later chapter that the use of two tracer gases provides a criterion for the rejection of non-representative data.

The following brief summary describes how these procedures were integrated into the experiment. The mother breathed a gas mixture containing N_2O, and the C_2H_2 was introduced into the blood being pumped into the placenta of a near term goat fetus via the umbilical arteries. The ratio of the umbilical to uterine blood flow was held constant until the rate of N_2O and C_2H_2 transfer across the placenta did not change with time. Samples were then drawn from a maternal carotid artery, uterine vein, umbilical artery and the mixed blood from a pair of umbilical veins. Several sets of samples were obtained at various flow ratios from one preparation and analyzed for N_2O and C_2H_2. Extreme flow ratios were obtained with the CO technique of Metcalfe et al. (59). The T^MT^F coordinates for N_2O and C_2H_2 were calculated for each set of samples and plotted on a T^MT^F diagram. The following sections describe

these procedures in detail.

B. SURGICAL PREPARATION

Domestic goats were used between the 100th and 140th day of gestation. Breeding dates were provided with all animals. X-rays were taken early in the fourth month of the pregnancy so that the number of fetuses could be determined. Twin pregnancies were chosen wherever possible. Food was withheld for 48 hours and water withheld for 24 hours before surgery. Each animal was weighed on the morning of the study and given 1 mg./kg. body weight of ethylisobutrazine hydrochloride (Diquel. Jensen-Salsbery Laboratories) by the intravenous route for pre-operative tranquilization. The anterior neck area, the entire abdomen and the left paradorsal area cephalad to the iliac crest were shaved.

A skin wheal of 2% lidocaine hydrochloride (Lidocaine. Invenex) was injected over a jugular vein. A polyvinyl catheter filled with heparinized saline (1000 USP per ml. Lipo-Hepin. Ricker Laboratories 2 ml. per 500 ml. saline) was inserted into the jugular vein through a 14 gauge thin-walled needle. The needle was removed and the catheter tied in position. A little heparinized saline was allowed to flow through the catheter to prevent clotting at the tip.

Two square inches of the anterior neck area were infiltrated with 2% lidocaine hydrochloride in the midline. The trachea

was exposed and elevated. A cruciate incision was made dividing two cartilagenous rings. A right angle brass tracheal cannula was inserted into the trachea and tied in position. The foregoing procedures were performed under local anesthesia because the goat is prone to rapid regurgitation and aspiration of rumen contents with the onset of general anesthesia. The goat remained standing during the tracheotomy and showed no signs of discomfort. When the tracheal cannulation was completed, general anesthesia was induced slowly with 8 to 12 mls. of a 5% solution of sodium thiamylal (Surital. Parke, Davis and Co.). Anesthesia was maintained with an intravenous gravity drip of 1% of sodium thiamylal in saline administered through the jugular venous catheter. The depth of anesthesia was estimated by lightly tapping the eyelid. When no blink reflex was elicited the plane of anesthesia was judged to be too deep. When a vigorous blink reflex was elicited the plane of anesthesia was judged to be too shallow.

The animal was lifted onto an operating table. A carotid artery was exposed through the anterior neck incision. A No. 12 Bardic catheter was inserted into the carotid artery flushed with heparinized saline and tied in place. A femoral artery was exposed and cannulated with a No. 14 Bardic catheter. In 5 goats, both femoral arteries were cannulated with No. 14 Bardic catheters to permit the measurement of the maternal shunt.

The left paradorsal area cephalad to the iliac crest was exposed and a 10 cm. longitudinal incision just lateral to the tips of the spinal transverse processes was made through skin, subcutaneous fat, and a superficial layer of transverse muscle into the retroperitoneal space. The dorsal aorta was exposed by blunt dissection in the region between the renal arteries and the bifurcation and carefully isolated on tape away from the adjacent vena cava. The two ends of the tape were threaded through a 30 cm. length of Tygon tubing (outside diameter 1·5 cm.) one end of which rested on the aorta. By this means the systemic arterial pressure below the tape could be reduced by drawing up on the tape and pushing down on the tubing to partially occlude the aorta. The extent of the occlusion was judged by a comparison of femoral and carotid arterial pressures.

The goat was lifted into a bath containing 150 liters of Kreb's solution ($NaHCO_3^-$ replaced by NaCl) maintained at 39° C. A canvas sling kept the animal immersed to the level of the lower rib cage. The upper border of the pregnant uterus was identified by palpation and a transverse incision 18 inches long was made in the abdomen and extended into the peritoneal cavity. One uterine horn was delivered into the incision so that the pattern of radial uterine veins draining into a main arcuate vein in the broad ligament could be identified. A radial vein on the distal portion of the horn

was selected for catheterization. Spasm of the vein was reduced with subserosal injection of 1% hexylcaine hydrochloride (Cyclaine. Merck, Sharp and Dohme). The adventitia was stripped from the vein which was elevated on two 4-0 silk ties and ligated distally. A polyvinyl catheter 50 cms. in length was inserted into the vein and advanced until the tip could be palpated in the common uterine vein 2 - 3 cms. dorsal to the ovary. The catheter was then tied in place. The contralateral common uterine vein was similarly catheterized. All catheters were regularly flushed with heparinized saline to prevent clotting.

At this stage a gas mixture of 50% oxygen, 50% N_2O was administered to the mother with a Bird respirator.

The fetus in one horn of the uterus was palpated to establish its position. The shape of the lumbar spine with its broad, heavy transverse processes was found to be a helpful landmark. The fetus was moved within the uterus by traction to an avascular area on the fundal or dorsal surface of the uterus. The fetal pelvis was held in this position and a 3-4 cm. incision was made through the serosa and myometrium, between attachments of individual cotyledons. The allantois and amnion were incised and the edges of the incision were fixed to the edges of the myometrial incision with Allis clamps. The lower abdomen of the fetus was then rotated toward the uterine incision and the umbilical cord looped out into the

bath on a finger. The cord was immediately injected with 3-4 ml. of 1% hexylcaine hydrochloride and 4-5 ml. of 1:10 formaldehyde to prevent umbilical vessel spasm. An umbilical vein was then injected with 1500 USP units of heparin (1000 units per ml.) using a 25 gauge needle. Each of the four cord vessels was dissected out at a point about 5 cm. from the abdominal wall of the fetus and elevated on tapes. Catheters were placed in both umbilical arteries and both umbilical veins so that blood could be pumped through the placenta via the umbilical arterial catheters and the venous drainage from the placenta collected from the umbilical venous catheters. All four cannulae were taped together to maintain their longitudinal orientation with relation to the cord. Blood was pumped into each umbilical artery at a low rate of flow as soon as each arterial catheter was tied in place. The stump of the cord was completely severed at the abdominal wall of the fetus, and the umbilical cord and fetus were replaced into the amniotic cavity. Very little fluid was lost during this procedure. The short incision in the endometrium was closed with running silk sutures. When a second fetus was present in the opposite horn it was treated in an identical manner to permit perfusion of the second placenta. On completion of these procedures the uterus was replaced into the maternal peritoneal cavity and the abdominal wall closed with towel clips. The time required to complete the surgical preparation

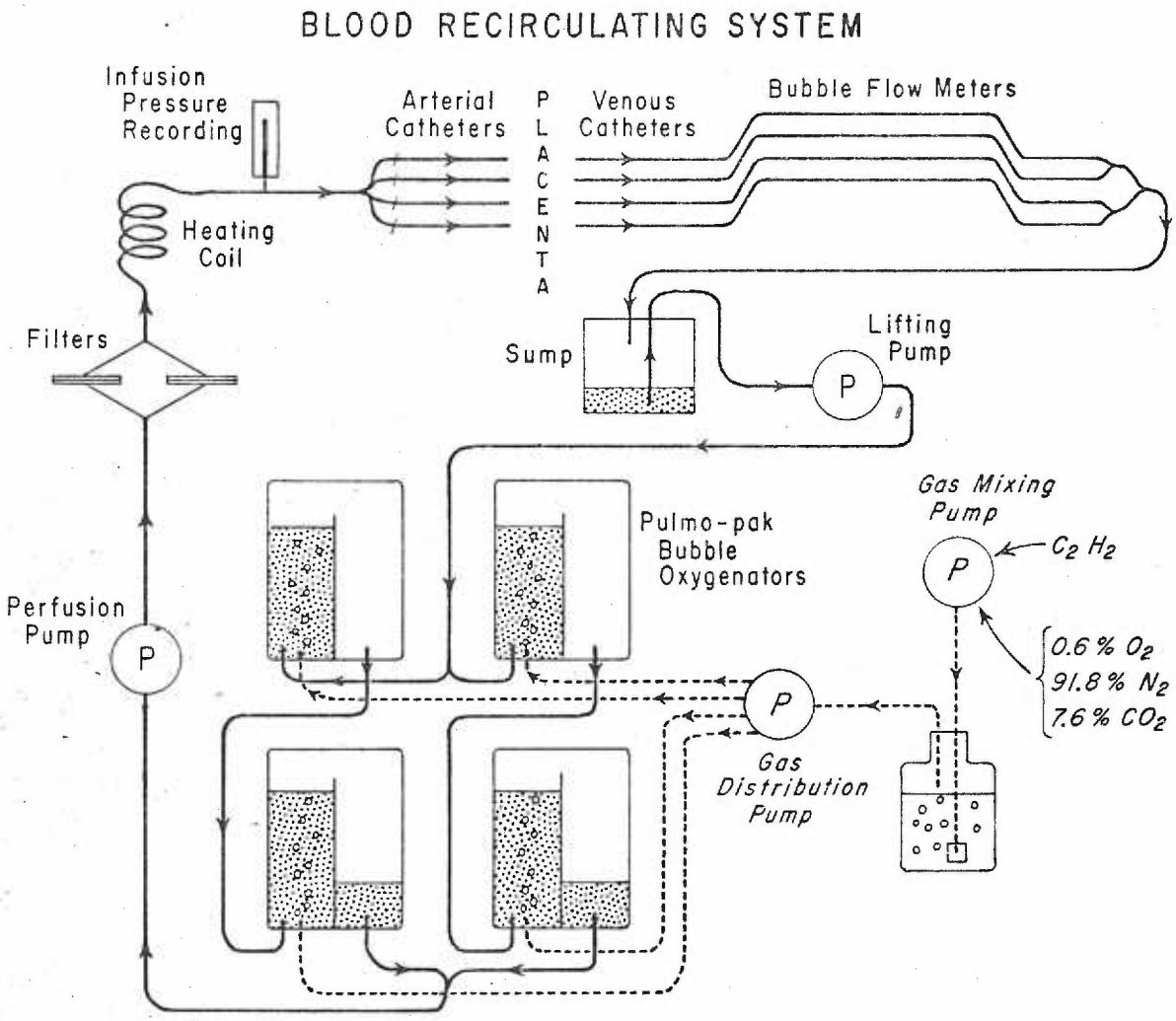
varied from 3 to 5 hours.

B. PERFUSION AND RECIRCULATION

The system is shown in Figure 8. Each umbilical venous catheter led to a glass tube (I. D. 7 mm.) which served as a bubble flowmeter. The glass tubes were connected together in parallel and the whole venous outflow drained into a small reservoir which could be moved in a vertical plane. During the perfusion the flow in the glass tubes was visualized with air bubbles of about 1 cc each and the sump moved down until intermittent flow was observed. The sump was then raised 2 cm. The intermittent flow was taken as an indication that the umbilical veins were collapsing. The raising of the sump then ensured that the pressure in the umbilical veins adjacent to the catheter tip was plus 1 or 2 mm. Hg.

A Harvard reciprocating pump, Model #1405, was used to lift the blood from the sump to the upper pair of 4 disposable bubble oxygenators (Pulmo-Pak, Abbott Labs). After passing though the upper pair the blood flowed by gravity through a lower pair, the outflow sections of which acted as the main reservoirs for the system. These reservoirs held 1·5 liters. Although they were intended to be disposable, it was possible to use the bubble oxygenators for 4 or 5 experiments providing that they were cleaned with water only. Detergents rapidly removed the antifoam inside the bubble oxygenators resulting in uncontrollable foaming during the experiments. Blood

Fig. 8. Diagram of the perfusion circuit. Solid lines represent the flow of blood. Dotted lines represent the flow of gas.


BLOOD RECIRCULATING SYSTEM
Infusion
Pressure
Recording
Arterial
Catheters
PLACENTA
Venous
Catheters
Bubble Flow Meters
Heating
Coil
Filters
Sump
Lifting
Pump
P
Gas Mixing
Pump
$C_2 H_2$
Pulmo-pak
Bubble
Oxygenators
Perfusion
Pump
0.6 % O_2
91.8 % N_2
7.6 % CO_2
Gas
Distribution
Pump

was taken from the reservoirs by the perfusion pump, a Harvard reciprocating pump, model #1401. The output of this pump was passed through two filters in parallel, heated to 38·5° C and fed into the umbilical arterial cannulae. The pressure at the beginning of the arterial cannulae was monitored with a mercury manometer and a Statham strain gauge transducer. The manometer was used during the preparatory procedures because occlusion of the placental vessels could cause high pressures in the umbilical arteries under the constant flow conditions that prevailed. The development of these pressures could be quickly detected with an eye level manometer close to the animal and the pump speed varied accordingly. An overflow resistance was not found to be necessary.

The filters were constructed from 6 inch diameter plexiglass circles with 1/4 inch thickness of cotton wool as the filtering agent.

During the passage of blood through the cascade of bubble oxygenators, it was equilibrated at room temperature with a gas mixture consisting of 0·5% O_2, 6% CO_2, 68.5% N_2 and 25%C_2H_2. Preliminary experiments showed that at a blood flow of 250 ml/min, 85% of the contaminating N_2O could be stripped from the blood in one pass through one bubble oxygenator, hence, passage through two, in series, would be expected to remove 98%. In practice, the equipment functioned even better than expected and the outflow

from the 4 bubble oxygenators contained less than 1% of the inflowing N_2O.

The gas mixture was obtained by admitting a gas containing 7·6% CO_2, 0·6% O_2 and 91·8% N_2 into one cylinder of a specially made 2-cylinder Harvard respiratory pump and admitting pure acetylene into the other. The stroke volumes of the cylinders were 75 ml. and 25 ml., respectively. The resulting gas mixture was saturated with water vapor at room temperature and distributed equally to each of the 4 bubble oxygenators with a Sigma motor pump, incorporating 4 tubes. The exhaust from the bubble oxygenators was vented out of the window.

The stroke volume of the primary perfusion pump was measured before the experiment and fixed. Flow was determined by counting the rate of the pump. The system was filled with 3 liters of freshly drawn heparinized or citrated goat blood taken from other animals before the experiment. When the surgical procedures were completed the desired ratio of umbilical blood flow to uterine blood flow was approximated by setting the rate of the perfusion pump and occluding the maternal abdominal aorta until the femoral arterial pressure was at a predetermined value. A period of 30 min. was allowed for equilibrium of the exchanging gases to occur. In two experiments, serial samples were taken during this 30 minute period to prove that equilibrium did indeed occur. At the end of this

period simultaneous samples of blood were taken from the maternal carotid artery, both uterine veins, an umbilical artery (perfusion inflow) and the mixed blood from each pair of umbilical veins (perfusion outflow). All of these blood samples were aspirated anaerobically in 10 ml. heparinized, greased glass syringes, capped and stored in ice until analyzed.

At the end of each experiment an autopsy was performed to locate the position of the tip of each uterine venous catheter. Cesarean section and hysterectomy were performed and each placenta was inspected closely in situ, and after removal, for evidence of placental hemorrhage or separation associated with the perfusion. The weight of each fetus, each placenta and the uterus was recorded. A count was made of the number of cotyledons on each placenta.

D. PERFUSION WITH CARBON MONOXIDE-DEXTRAN-KREBS SOLUTION

In addition to these studies using N_2O and C_2H_2, the fetal and maternal shunts were determined by the method of Metcalfe et al. (59). The fetal shunt was obtained by replacing the blood in the perfusion circuit with Krebs solution ($NaHCO_3$ replaced by NaCl) containing dextran* (M W 80,000), 5% by weight, saturated with carbon monoxide. The maternal shunt was obtained by perfusing the placenta with the blood recirculating system as previously described and

* Dextran T - 80 was donated by Pharmacia Co., Uppsala, Sweden

pumping the CO - dextran - Krebs solution through a heat exchanger and into both femoral arterial catheters. The loop tie round the maternal abdominal aorta was drawn tight and the mother was killed to reduce the maternal arterial pressure to zero. The perfusate reached the uterine arteries by retrograde passage of the femoral arteries to the abdominal aorta. Pressure in the femoral arteries could be determined by monitoring the pressure in the femoral arterial catheter.

Ten liters of CO - dextran - Krebs solution were infused for each fetal shunt and 30 liters for each maternal shunt. Serial samples of infusate and fetal or maternal venous outflow were drawn to prove that equilibrium was achieved with the shunted flows and the steady state was obtained.

F. ANALYSES

The N_2O and C_2H_2 concentration in the blood samples was measured with a Beckman GC - 2A gas chromatograph with blood gas accessory. The blood gas accessory permits the mixing of 0·1 ml. samples with 0·5 ml. of a ferricyanide - saponin reagent to lyse the erythrocytes and oxidize the hemoglobin. The reacting mixture of sample and reagent is stirred in a reaction tube with a volume of 10 ml. for 1 minute in an atmosphere of helium. During this time most of the dissolved gases in the sample diffuse into the helium atmosphere of the reaction tube. At the end of 1 minute the reaction

tube is coupled to the helium flowing through the columns of the gas chromatograph. This helium bubbles through the mixture of sample and reagent thereby stripping out any residual gases other than helium. This is the inject phase of the analysis and lasts for 30 seconds. At the end of this time the reaction tube is discarded for cleaning. The gases, extracted from the sample, are carried through the columns of the gas chromatograph by the helium stream. A thermal conductivity cell at the exit of the columns was used as the detector. The qualitative analysis was obtained from the time it took to reach the detector (elution time) and the quantitative analysis obtained by measuring the response of the detectors with a strip chart recorder. The analysis of N_2O and C_2H_2 was best performed with the following instrument settings:

Carrier gas flow - 80 ml. /min.

Column type - 4 foot Silica gel.

Filament Current - 220 millamperes.

Column temperature - 160° C.

Attenuation - 1X to 5X.

At these settings the elution time of N_2O was 80 seconds and the elution time of C_2H_2 was 140 seconds. The instrument was not calibrated in absolute units and results were expressed in peak height units only.

At the above settings of the instrument the resolution was

satisfactory. Experimental arterial blood levels of N_2O and C_2H_2 gave close to full scale deflection at an attenuation of 2X with a sample size of 0·1 ml. It was desirable to keep the sensitivity of the instrument as low as possible yet have the lowest venous concentration of N_2O or C_2H_2 give a response of at least 30% of full scale deflection at an attenuation of 1X. Excessively high sensitivity, as determined by the filament current, caused the baseline to drift but the most serious side effect was oxidation of the filaments. The blood samples carried up to 15 volumes per cent of oxygen. Under the conditions of the analysis this gas was eluted very rapidly and reached the filaments in relatively concentrated form. During the pilot studies several sets of filaments were irreversibly damaged due to oxidation and it was found that 220 millamperes was the maximum filament current that could be tolerated when analyzing blood samples of 0·1 ml. The same set of filaments was used for the analysis of all samples reported in this study and there was no evidence of decreased sensitivity during this period. The sample size and instrument sensitivity being fixed, it was necessary to obtain the desired resolution by altering the amount of gas in the arterial blood of the preparation. A maternal breathing mixture containing 50% N_2O and a bubble-oxygenator inlet gas mixture containing 25% C_2H_2 were selected on this basis.

The presence of any gas other than N_2O or C_2H_2 with the same elution time as one of these gases would invalidate the analysis. Unfortunately CO_2 had the same elution time as N_2O under the conditions of the analysis. It was found that the use of an eight foot activated charcoal and hexadione column would separate N_2O and CO_2 but the elution times were excessively long. The CO_2 was removed from all samples by passing the carrier flow of helium from the blood gas accessory through a short length of tubing filled with a CO_2 absorbent (Ascarite, Arthur H. Thomas Co.). Tests showed that under the conditions of the analysis there was no detectable response to the CO_2 eluted from 0.1 ml. blood samples. The CO_2 absorbent was changed once a month.

When the instrument was properly maintained there was no detectable baseline drift. Such a drift could be caused by a change in temperature, helium flow, filament current, or by the elution of contaminants from the colums. The first three possible causes were apparently taken care of by the design of the instrument itself. The elution of contaminants from the column was prevented by reversing the column once a week and purging it with a high helium flow at 220° C.

The blood gas accessory has not been very useful in the analysis of blood gases due to air contamination in its main function valve. This does not affect the analysis of N_2O or C_2H_2. The

problem with blood gas analysis was not loss of sample but the addition of trapped air to the sample. Because the transfer of the extracted gases from the blood gas accessory to the column took place at a pressure of about 700 mm. Hg above ambient pressure the presence of a leak in the system, which would result in a loss of sample, was signalled by a drop in pressure and flow. This was visible as a changing baseline and an abnormally low reading of the on-line flowmeter attached to the exhaust of the instrument. When this occurred the reading was discarded.

The instrument was found to perform analyses with a standard deviation of less than 1% when the reading was near full scale deflection. The change in sensitivity with time was negligable as is shown in a holding-time trial discussed in the next chapter. To protect against possible transient changes in sensitivity all samples of each set were analyzed before commencing the analysis of the next set of samples. It was usual to repeat the analysis of the first sample at the end of each day. At no time did this procedure demonstrate a significant change in sensitivity, over the eight hour operating period.

The analyses for N_2O and C_2H_2 were performed the day after the samples were obtained and a test was conducted to see how much gas was lost in this period of time from the sample syringes. No detectable change could be measured over a 24 hour

period and very little change was seen in 30 days under the conditions of the test.

The linearity of the instrument response to N_2O and C_2H_2 was tested by analyzing water containing these gases at a range of concentrations that encompassed those levels observed throughout the goat experiments.

The carbon monoxide analysis of samples obtained during the CO - dextran - Krebs solution perfusions were also performed on the Beckman GC-2A gas chromatograph. The following changes in procedure were necessary:

1. A 6 foot molecular sieve column was substituted for the 4 foot silical gel column.

2. The sample size was increased to 0·5 ml.

Under these conditions the elution time of carbon monoxide was 90 seconds. The linearity of the instrument response to CO was not examined because it was unlikely to be different from that for N_2O and C_2H_2.

The following analyses were performed on several samples from each experiment. Hemoglobin concentration was determined by the colorimetric determination of cyanmethemoglobin with a Coleman Junior Spectrophotometer. The linearity of the instrument was not tested. The standard deviation of serial determinations of the same sample was less than 2%. Calibration was achieved by the

use of a commercially available cyanmethemoglobin standard solution.

The P_{O_2}, P_{CO_2} and pH were measured with a Radiometer micro-electrode assembly. The pH electrode was calibrated with commercially available standard buffer solutions at pH's of 6·840 and 7·381. The standard deviation of successive measurements of the same sample was less than 0·01 pH units. The P_{O_2} and P_{CO_2} electrodes were calibrated with saturated gases at 39° C with a known content of oxygen and carbon dioxide. Oxygen and CO_2 analyses of the calibration gases were performed on a Scholander gas analyzer, the calibration and sensitivity of which is reported by Scholander (76). Duplicate readings agreeing within 0·02 volumes per cent of each other were considered sufficient. The P_{O_2}, P_{CO_2} and pH electrodes were calibrated after every fourth sample.

The accuracy of the P_{O_2}, P_{CO_2} and pH measurements made during this study was less than that of which the Radiometer was capable. The time available for these analyses forced the results to be limited by the following criteria. Duplicate measurements of pH within 0·015 pH units of each other were accepted. Duplicate measurements of P_{O_2} and P_{CO_2} within 2 mm. Hg of each other were accepted. These limitations were necessary because the surgical and experimental procedure took 8 hours. The

above mentioned analyses were therefore performed by an operator working at suboptimal levels of effectiveness.

RESULTS

A. Linearity of the gas chromatographic response to nitrous oxide and acetylene

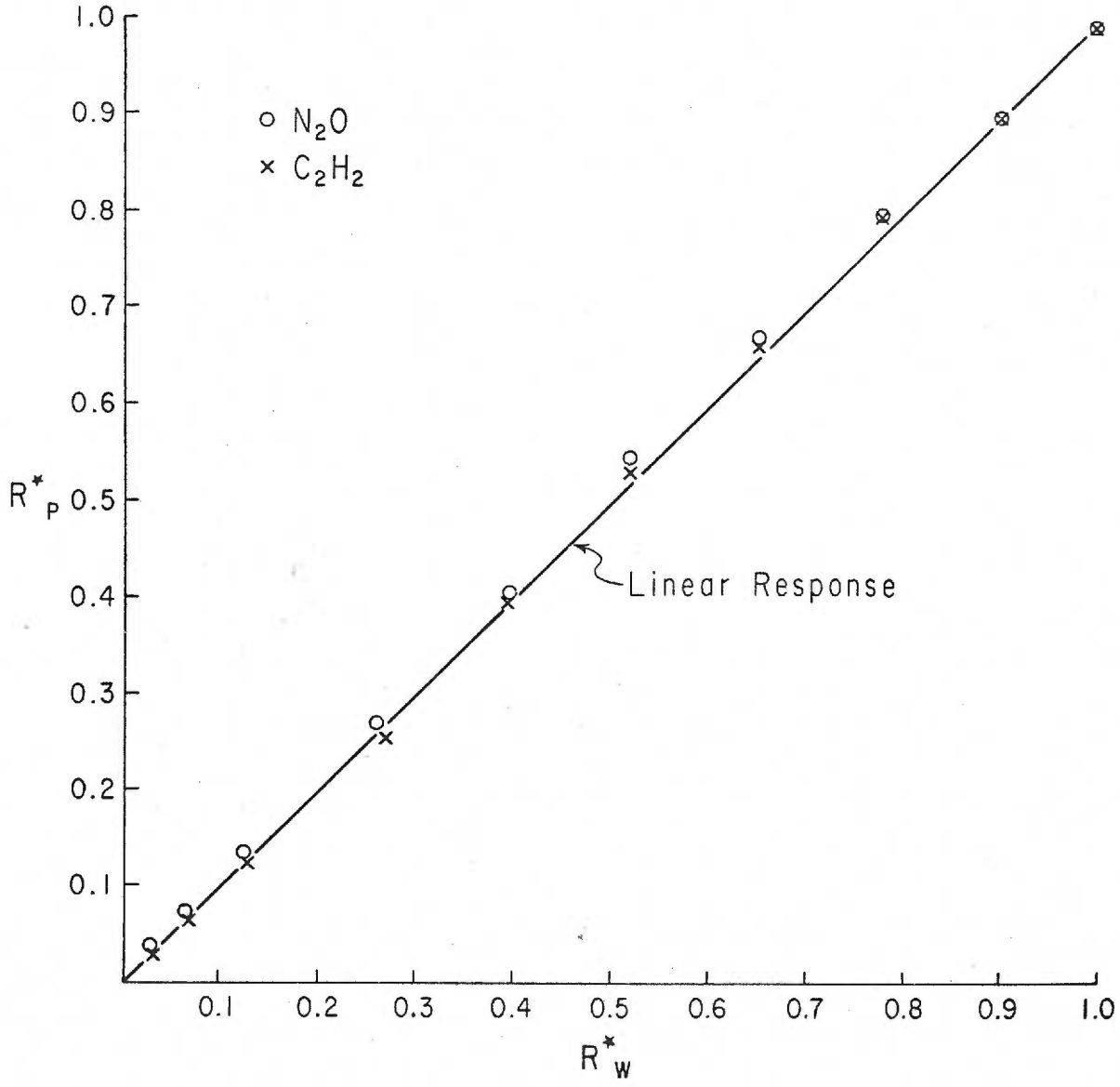
The results of this trial are shown in Figure 9. The ordinate represents the response of the instrument to various amounts of N_2O and C_2H_2 and the abscissa represents the amount of these gases that was predicted to be present. It can be seen that the deviation of the points for N_2O and C_2H_2 from the straight line that represents linearity in this plot has a maximum value of 4%. This small deviation is probably due more to weighing error than non-linear instrument response. The axes require more explanation. The ordinate R^*_P is the ratio of the peak heights of N_2O or C_2H_2 obtained from an analysis of a particular sample to the peak heights of N_2O or C_2H_2 obtained from the sample containing the most N_2O and C_2H_2, sample number 1. This latter sample has an R^*_P value of 1. All other samples were dilutions of the fluid used to fill syringe number 1 and have R^*_P values of less than 1.

The abscissa R^*_W is a more complex quantity because the weighings had to be done under anaerobic conditions. Three weights were required to evaluate R^*_W for each syringe.

Wt. # 1 = Weight of syringe + mercury + syringe cap.

Wt. #2 = Wt. #1 + weight of pure water required to fill the dead space of the syringe and to dilute the water containing N_2O

Fig. 9. Linearity of the Beckman GC-2A response to N_2O and C_2H_2. The ordinate (R^*_P) represents the instrument response to each sample as a fraction of the response to the sample with the most N_2O and C_2H_2. The abscissa (R^*_W) represents the amount of N_2O and C_2H_2 in each sample as a fraction of the amount in the sample with the most N_2O and C_2H_2. The solid line is the line of absolute linearity.


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
R*P
○ N2O
× C2H2
Linear Response
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
R*W

and C_2H_2.

Wt. #3 = Wt. #2 + weight of the water containing N_2O and C_2H_2 added to the syringe.

For each of the 9 syringes the weight of water containing N_2O and C_2H_2 (G) = #3 - #2 and the total amount of water (W) = #3 – #1. It follows that for each syringe, the ratio of contained N_2O and C_2H_2 to the amount of these gases in syringe number 1 is R^*_W. Where R^*_W is equal to G/W for that syringe times K and K = #3 - #1/ #3 - #2 for syringe number 1.

The value K is included in the calculation of R^*_W because the dead space of syringe number 1 had to be filled with pure water before the water containing N_2O and C_2H_2 could be added anaerobically. It can be seen that R^*_W for syringe number 1 is equal to #3 - #2/ #3 - #1 for sample number 1 times #3 - #1/ #3 - #2 for sample number 1 which is equal to 1. In this way for sample number 1, $R^*_W = R^*_P = 1$. The line denoting complete linearity of response was drawn from this point to the origin.

B. Time dependent changes in N_2O and C_2H_2 concentrations after sampling

The analyses for N_2O and C_2H_2 were performed on the day after the experiment. It was possible that some of these gases leaked from the syringes overnight. To test this possibility eight 10 ml. syringes were greased and filled with water containing

N_2O and C_2H_2. These syringes were then sealed and stored in ice, the preparation and storage being exactly the same as that used during the handling of blood samples. The syringes were analyzed for N_2O and C_2H_2 at the times of filling and at various subsequent times. The results of these analyses are shown in table 6.

TABLE 6

Effect of time on the N_2O and C_2H_2 concentrations in syringes under the experimental conditions. N_2O and C_2H_2 concentrations expressed as peak heights.

Syringe number		0	Day 1	Day 2	Day 4	Day 9	Day 30
1	N_2O	380	380	380	385	380	380
	C_2H_2	285	285	290	280	280	280
2	N_2O	345		330		340	340
	C_2H_2	257		260		255	255
3	N_2O	305	300		300		
	C_2H_2	225	222		225		
4	N_2O	260		255			
	C_2H_2	190		184			
5	N_2O	210	205		200		
	C_2H_2	152	148		144		
6	N_2O	154				154	154
	C_2H_2	114				112	112
7	N_2O	102	102				
	C_2H_2	72	72				
8	N_2O	26	26				
	C_2H_2	15	15				

It can be seen that for a period of 30 days there was no detectable decrease in the amount of N_2O or C_2H_2 in the syringes. Small fluctuations in the day to day responses probably reflect analytical errors because there is no overall downward trend in the changes. All analyses were done under the same conditions and at the instrument settings used during the analyses of blood samples. It is apparent that holding samples overnight does not result in any loss of N_2O and C_2H_2 under the conditions of this experiment. Table 6 also demonstrates the stability of the sensitivity of the gas chromatograph.

C. Time of sampling

The blood samples cannot be taken as soon as the desired flow ratio is established in the preparation because it would take some time for the N_2O and C_2H_2 concentrations in the venous outflows to reach a stable level. The length of time taken would depend on the volume of fluid between the capillary bed and the sampling site and on the rate of blood flow in the system among other things. These factors were unknown at the time of sampling. An arbitrary period of 30 minutes was decided on and in two experiments serial samples were taken from uterine and umbilical veins during this time to check that stability was achieved. The results of these experiments cannot be averaged because the blood flows and volumes were not the same in each vessel sampled.

Equilibrium was achieved in all cases. A representative set of results is shown in Figure 10. It can be seen that the time course of the change in N_2O concentration is the same as that for C_2H_2. The half time of the change was close to 2 minutes and 90% of the change had occurred within 10 minutes. Equilibrium was essentially established within 30 minutes because the 30 minute sample was not different from the 25 minute sample.

The time course of changes in the umbilical venous concentrations of N_2O and C_2H_2 was the same as that for the uterine veins.

D. Organ weights

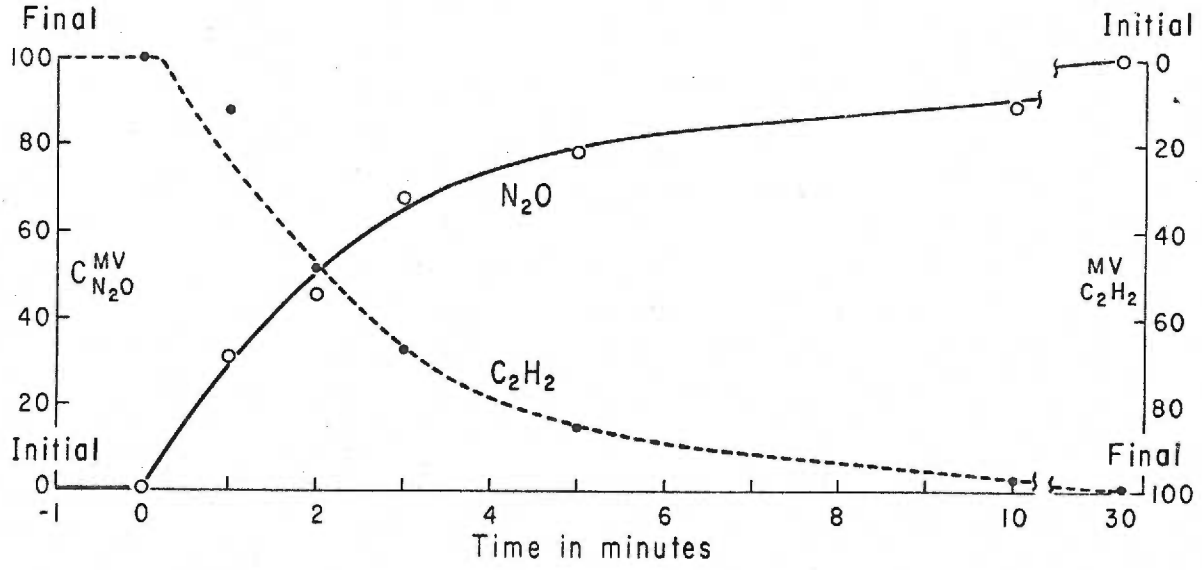
The wet weights of the various tissues and the ages of the fetuses are given in appendix 5. These results are summarized in table 7.

TABLE 7

Mean wet weights, number of cotyledons per placenta and ages of 10 single and 20 twin fetuses from 20 goats.

Category	Single pregnancies	Twin pregnancies
Fetal Weight	1934 gms.	1779 gms. ea.
Uterine Weight	1028 gms.	1134 gms.
Placental Weight	1099 gms.	593 gms. ea.
Number of Cotyledons	113.	74. ea.
Weight of Mother	50.5 kgs.	52.8 kgs.
Age of Fetus	129 days	123 days

Fig. 10. Time course of the change in concentration of N_2O and C_2H_2 in a uterine vein following a change in flow ratio from 1·0 to 0·25. The ordinate on the left is initial to final concentration of N_2O. The ordinate on the right is final to initial concentration of C_2H_2.


Final
Initial
100
80
60
40
20
0
$C^{MV}_{N_2O}$
N_2O
C_2H_2
$MV_{C_2H_2}$
Initial
Final
-1
0
2
4
6
8
10
30
Time in minutes

It can be seen that the placentas of the twin pregnancies are only 54% of the weight of placentas from single pregnancies. In spite of this fact there were no observable differences between twin and single placentas as defined by subsequent N_2O and C_2H_2 analyses.

E. Respiratory gas status

Measurements were made of the P_{O_2}, pH and P_{CO_2} of the blood samples drawn for N_2O and C_2H_2 analysis whenever possible. Such measurements were made on the day of the experiment and the samples were kept on ice during the 2 to 3 hour storage period. These data are presented in appendix 1 and are summarized in table 8.

TABLE 8

A comparison of the respiratory gas status of the perfused preparation and that of the intact pregnant goat as defined by the literature.

	Data from Perfusions	Established Values for the Goat	Reference
FA P_{O_2}	16(sd 10) mm. Hg	17 mm. Hg	14
FA pH	7.06(sd 0.15)	7.20	14
FA P_{CO_2}	49(sd 20) mm. Hg	46 mm. Hg	15
MA P_{O_2}	120(sd 24) mm. Hg	84 mm. Hg	15
MA pH	7.37(sd 0.09)	7.39	14
MA P_{CO_2}	31(sd 8) mm. Hg	36 mm. Hg	15

It would have been desirable to obtain measurements of oxygen concentration in these samples but this was not possible in the time available. In theory it should be possible to calculate the oxygen content of each sample because a nomogram relating the pH, P_{O_2} and percentage saturation of the hemoglobin with oxygen is available for goat blood (39). The per cent saturation and hemoglobin concentration are normally sufficient to provide the oxygen concentration. This prodecure would be valid as applied to the maternal blood samples but not to the blood used to perfuse the fetal side. The perfusing blood had been stored for 24 hours before the experiment. This, in itself, would seriously compromise the accurate use of a nomogram representing freshly drawn goat blood. A further problem is posed by the fact that for several experiments the blood was drawn into donor sets containing ACD buffer which resulted in some hemolysis. Later experiments involved blood drawn into donor sets containing heparin as the anticoagulant and hemolysis did not occur. For these reasons samples number 3 - 139 had some degree of hemolysis in the samples from the perfusate while samples number 140 - 305 were not hemolyzed at all. The nomogram would not be at all accurate as applied to partially hemolyzed blood. In the light of these facts the conversion of the data from P_{O_2} to oxygen content was not made.

F. Nitrous oxide and acetylene data

One hundred and twenty sets of blood samples were taken from each of the following vessels, the maternal carotid artery (MA), uterine vein (MV), umbilical artery (FA) and the umbilical vein (FV) during the perfusion of 23 placentas in 14 goats. These blood samples were analyzed for N_2O and C_2H_2 the day after the experiment. The T^M and T^F coordinates for N_2O and C_2H_2 were calculated for each set of samples where, $T^M = (C_{MA} - C_{MV}) / (C_{MA} - C_{FA})$ and $T^F = (C_{FV} - C_{FA}) / (C_{MA} - C_{FA})$. The notation C represents the concentration of N_2O or C_2H_2 in the sample expressed in peak height units. The gas chromatograph was not calibrated because the calibration factor would have appeared in both the numerator and denominator of both equations.

The T^M and T^F values for N_2O were rarely exactly the same as those for C_2H_2 from the same set of samples. The mean $T^M T^F$ coordinates were defined as: $\bar{T}^M = 1/2\ (T^M_{N_2O} + T^M_{C_2H_2})$; $\bar{T}^F = 1/2\ (T^F_{N_2O} + T^F_{C_2H_2})$. The possible causes of this divergence will be discussed in the next chapter.

Under ideal conditions T^M and T^F should be the same for both gases. It was arbitrarily decided to reject all those sets of data in which the distance between the $T^M T^F$ point for nitrous oxide and the $T^M T^F$ point for acetylene was greater than 0·1. This distance (X) is given by the equation:

$$X = \left(\left(T^{M}_{N_2O} - T^{M}_{C_2H_2} \right)^2 + \left(T^{F}_{N_2O} - T^{F}_{C_2H_2} \right)^2 \right)^{1/2}$$

In this manner 36 sets of data points were rejected representing 29% of all data obtained. The N_2O and C_2H_2 analyses of the samples representing the remaining 84 sets of data are given in appendix 2. The T^M and T^F points calculated from the data in appendix 2 for N_2O and C_2H_2 are given in appendix 3. Appendix 3 also contains the means of the N_2O and C_2H_2, $T^M T^F$ values, ($\bar{T}^M$ and $\bar{T}^F$), the values for the flow ratios (R^M) calculated from the formula $R^M = T^M/T^F$ and the mean flow ratios ($\bar{R}^M$) calculated from the formula $\bar{R}^M = \bar{T}^M/\bar{T}^F$.

The method of calculating the $T^M T^F$ coordinates from the N_2O, C_2H_2 data in appendix 2 is illustrated for the 18th experiment. Goat number 18 carried twin fetuses and the two placentas are designated "right" and "left".

Table 9 gives the N_2O and C_2H_2 analyses obtained from the 4 vessels at three different flow ratios.

TABLE 9

N_2O and C_2H_2 content of blood drawn from the maternal (MA) and umbilical (FA) artery and right (R) and left (L) uterine (MV) and umbilical veins (FV) of placental perfusion number 18 at three different ratios (R^M) of umbilical to uterine flow ($\dot{Q}_F/\dot{Q}_M$). Contents are expressed as peak heights.

Datum Number	Placenta + Run	MA		MV		FA		FV	
		N_2O	C_2H_2	N_2O	C_2H_2	N_2O	C_2H_2	N_2O	C_2H_2
185	R - 1	247	3	143	56	8	140	84	102
187	L - 1	247	3	160	47	8	140	87	101
197	R - 2	217	3	182	45	5	164	120	79
199	L - 2	217	3	177	35	5	164	106	85
209	R - 3	220	3	187	30	2	166	112	83
211	L - 3	220	3	185	27	2	166	115	83

Table 10 illustrates the results of the first step in the calculation of T^M and T^F. In this table, three concentration differences are shown. The maternal arterial to venous concentration difference, the fetal venous to arterial concentration difference and the maternal to fetal arterial concentration difference. The T^M and T^F values can be calculated for N_2O and C_2H_2 for each placenta at each flow ratio from the data given in table 10.

TABLE 10

The concentration differences required for the calculation of T^M and T^F for three flow ratios in the two placentas, (right (R) and left (L)) of experiment 18. (MA - MV) The maternal arterio-venous concentration difference. (FV - FA) The fetal venous-arterial concentration difference. (MA - FA) The maternal-fetal arterial concentration difference. The differences are given as differences in peak heights for N_2O and for C_2H_2.

Placenta + Run	(MA - MV)		(FV - FA)		(MA - FA)	
	N_2O	C_2H_2	N_2O	C_2H_2	N_2O	C_2H_2
R - 1	104	-53	76	-38	239	-137
L - 1	87	-44	79	-39	239	-137
R - 2	35	-43	115	-85	212	-161
L - 2	40	-32	101	-79	212	-161
R - 3	33	-27	110	-83	218	-163
L - 3	35	-24	113	-83	218	-163

The results of these calculations together with the calculated values for $\bar{T}^M$, $\bar{T}^F$ and X are shown in table 11.

TABLE 11

The values of T^M and T^F for N_2O and C_2H_2 ($T^M_{N_2O}$, $T^F_{N_2O}$, $T^M_{C_2H_2}$, $T^F_{C_2H_2}$), the mean values of T^M and T^F ($\bar{T}^M$ and $\bar{T}^F$) and the distance (X) between the $T^M T^F$ points for N_2O and those for C_2H_2 for three flow ratios in the two placentas, right (R) and left (L), for experiment 18.

Placenta + Run	$T^M_{N_2O}$	$T^M_{C_2H_2}$	$T^F_{N_2O}$	$T^F_{C_2H_2}$	$\bar{T}^M$	$\bar{T}^F$	X
R - 1	0.44	0.39	0.32	0.28	0.41	0.30	0.06
L - 1	0.37	0.32	0.33	0.28	0.34	0.31	0.07
R - 2	0.17	0.26	0.54	0.53	0.22	0.53	0.09
L - 2	0.20	0.20	0.48	0.49	0.20	0.48	0.01
R - 3	0.15	0.17	0.50	0.51	0.16	0.51	0.02
L - 3	0.16	0.15	0.52	0.57	0.15	0.54	0.05

The three flow ratios observed during experiment 18 were obtained by manipulating the uterine arterial pressure (MAP) and the umbilical arterial pressure (FAP). These manipulations produced concommitent changes in the umbilical ($\dot{Q}_F$) and uterine ($\dot{Q}_M$) blood flows. Table 12 shows the relevant pressures and the resulting flows and flow ratios that were required to produce the conditions at which the data shown in table 9 were obtained. The uterine flow $\dot{Q}_M$ is calculated from the relationship $\dot{Q}_M = \dot{Q}_F / R^{\bar{M}}$

and only represents blood flow to half of the uterus. The whole uterine blood flow being the sum of the uterine flow associated with the right placenta and that associated with the left placenta.

TABLE 12

The femoral arterial pressures (MAP) and umbilical arterial pressures (FAP) and the concommitant umbilical blood flows ($\dot{Q}_F$) and uterine blood flows ($\dot{Q}_M$) and ratios of umbilical to uterine blood flows (R^M) required to produce the conditions under which the data, shown in table 9, were obtained.

Placenta - Run	$\dot{Q}_F$ ml./min.	$R^M_{N_2O}$	$R^M_{C_2H_2}$	$\bar{R}^M$	$\dot{Q}_M$ ml./min.	FAP mm. Hg	MAP mm. Hg
R - 1	204	1.37	1.39	1.38	149	50	40
L - 1	195	1.10	1.13	1.12	174	50	40
R - 2	128	0.30	0.49	0.40	324	67	80
L - 2	170	0.40	0.40	0.40	425	67	80
R - 3	101	0.30	0.32	0.31	322	63	70
L - 3	100	0.31	0.31	0.28	353	63	70

The T^MT^F plot of the data obtained in table 11 is shown in Figure 11. It can be seen from table 11 that none of the data were rejected, because the distance (X) between corresponding N_2O and C_2H_2 points is less than 0·1 for all data pairs.

Figure 12 shows the mean T^MT^F points ($\bar{T}^M$ and $\bar{T}^F$) for the 85 acceptable data pairs contained in appendix 3. This figure

Fig. 11. $T^{M}{}_{T}{}^{F}$ plot of the N_2O and C_2H_2 data pairs obtained from the right and left placentas of goat # 18 at 3 different flow ratios. The raw data and calculations necessary to the acquisition of these $T^{M}{}_{T}{}^{F}$ coordinates are given in tables 9, 10 and 11. The conditions under which the data were obtained are given in table 12.

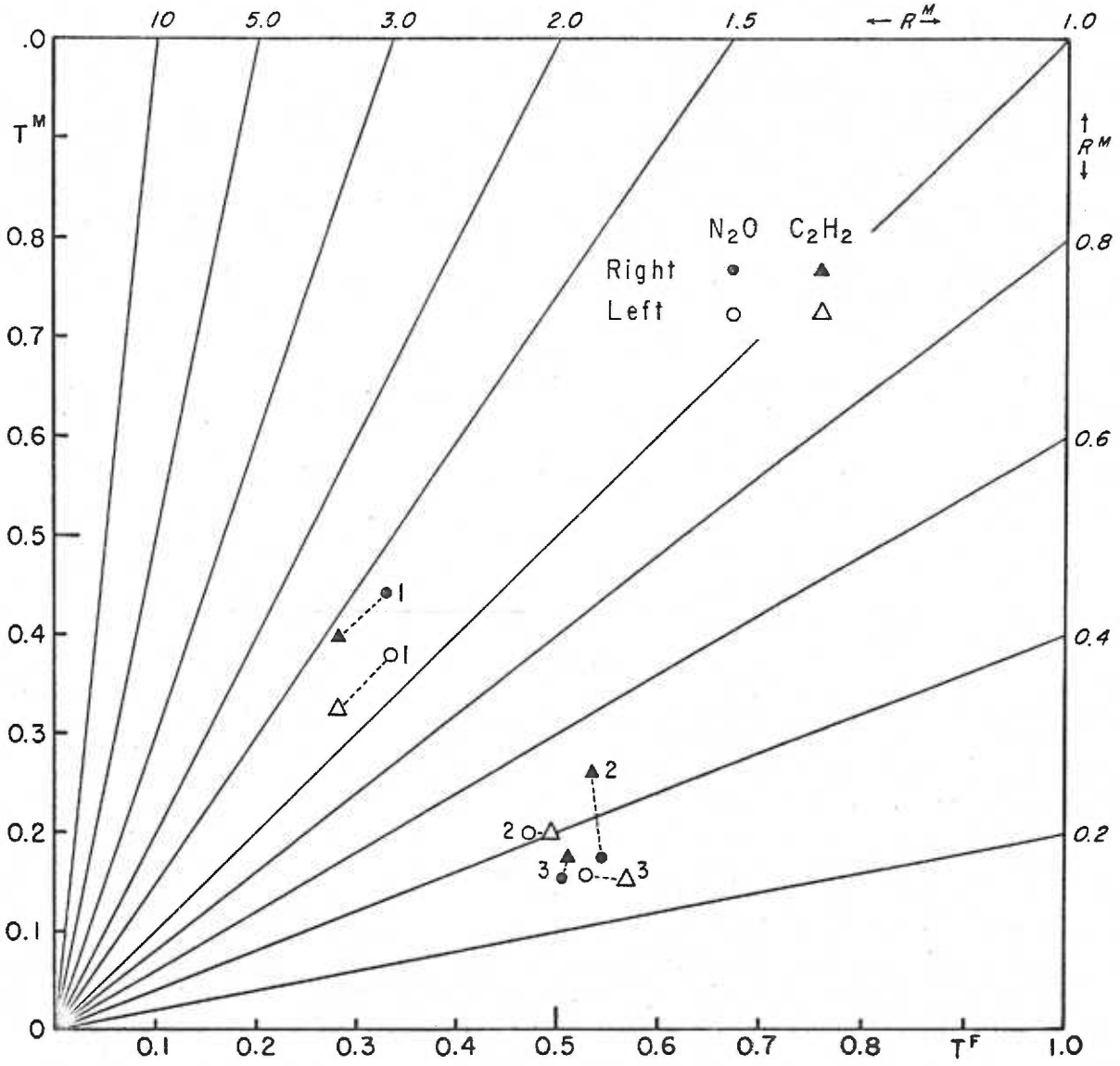
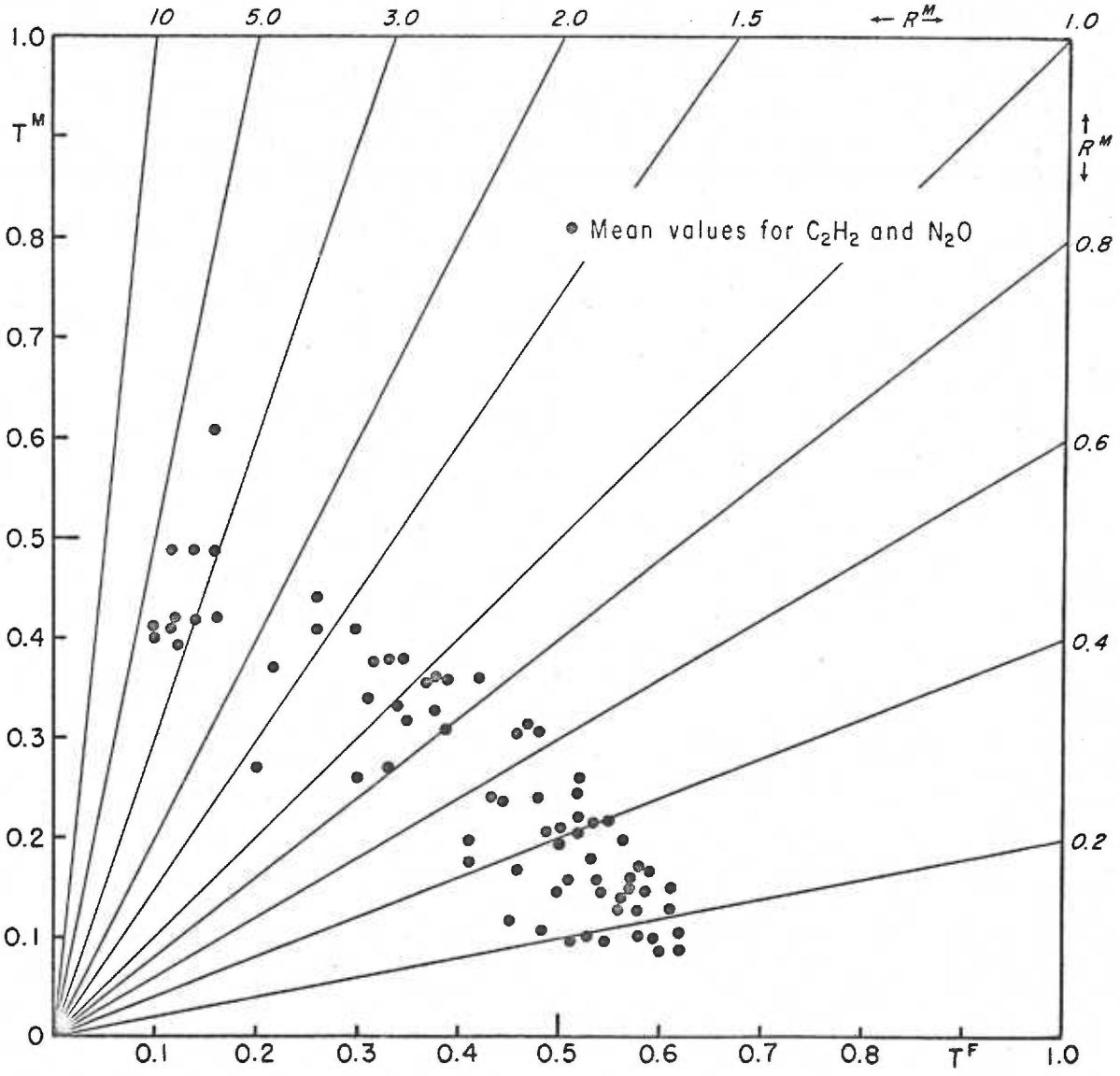

10
5.0
3.0
2.0
1.5
← R^M →
1.0
.0
T^M
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
↑ R^M ↓
0.8
0.6
0.4
0.2
N2O C2H2
Right
Left
1
1
2
2
3
3
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0

Fig. 12. $T^{M}T^{F}$ plot of the means of the 85 N_2O and C_2H_2 data pairs that are less than 0·1 scale units apart. ($\overline{T}^{M}$ and $\overline{T}^{F}$) obtained by perfusing 23 near term goat placentas at various ratios of umbilical to uterine blood flow.


10
5.0
3.0
2.0
1.5
← R^M →
1.0
1.0
T^M
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
↑ R^M ↓
0.8
0.6
0.4
0.2
Mean values for C2H2 and N2O
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0

constitutes the primary result from all the experiments using N_2O and C_2H_2. Acceptable data were obtained over the range of flow ratios($\bar{R}^M$) from 0·17 to 4·80. These flow ratios were obtained by varying the umbilical arterial pressure (FAP) between 27 mm. Hg and 98 mm. Hg and the femoral arterial pressure (MAP) between 30 mm. Hg and 110 mm. Hg. In the course of these procedures the umbilical blood flow per placenta ($\dot{Q}_F$) ranged from 75 ml. /min. to 376 ml. /min. and the uterine blood flow associated with a single placenta ($\dot{Q}_M$) ranged from 35 ml. /min. to 2199 ml. /min. The hemodynamic data for each preparation is given in appendix 4. These data show how each individual flow ratio was obtained.

G. Carbon monoxide (CO) shunts

Twelve determinations of the fetal shunt were made on 4 placentas in 2 goats and 20 determinations of the maternal shunt were made on 8 placentas in 5 goats. The fetal shunt was found to be 23% (sd 2·2%), and the maternal shunt was found to be 36% (sd 3·9). The data pertaining to the calculation of the fetal shunt are shown in table 13.

Table 14 contains the data obtained during perfusion of the uterine circulation with CO-dextran-Krebs solution. Goat #16 carried a single fetus that was largely in one horn of the uterus. The uterine venous samples reported in table 14 for goat #16 are

TABLE 13

The fetal arterial and venous CO concentrations, expressed as peak heights, the fetal shunt calculated from these data and the umbilical flow rate of CO-dextran-Krebs solution obtained in 12 determinations of the fetal shunt made in 4 placentas in 2 goats.

Sample Name	Umbilical Arterial CO Peak Height	Umbilical Venous CO Peak Height	Fetal Shunt %	Umbilical Flow ml. /min.
13 - 1R	262	63	24	580
13 - 1L	262	68	26	580
13 - 2R	250	60	24	580
13 - 2L	250	69	28	580
15 - 1R	270	54	20	400
15 - 1L	270	63	23	400
15 - 2R	268	62	23	400
15 - 2L	268	60	22	400
15 - 23R	268	58	22	400
15 - 24R	268	57	21	400
15 - 21L	268	58	22	400
15 - 22L	268	56	21	400

TABLE 14

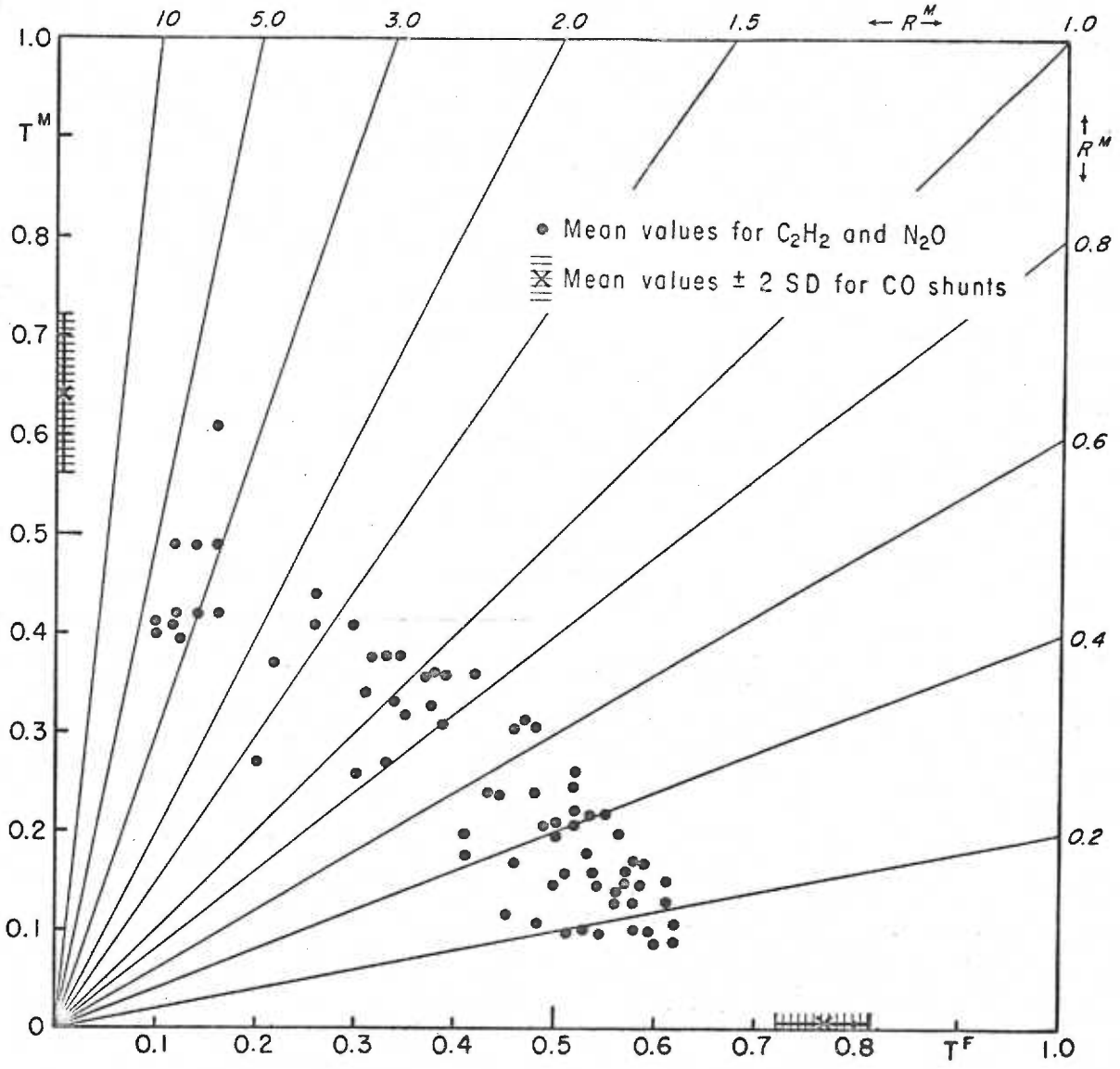
The maternal arterial and venous CO concentrations, expressed as peak heights, the maternal shunt calculated from these data, the amount of hemoglobin in the venous samples and the umbilical blood flows and flow rates of CO-dextran-Krebs solution obtained in 20 determinations of the maternal shunt in 8 placentas in 5 goats.

Sample Name	Uterine arterial CO peak height	Uterine venous CO peak height	Maternal shunt %	Femoral flow ml./min.	Hemoglobin conc. gm%	Fetal flow rate ml./min.
2-5	76	23	32	200	0.005	50
2-6	73	24	33	200	-----	75
3-3	90	31	34	300	0.001	75
3-4	90	31	37	300	0.001	80
4-4L	93	36	39	350	-----	80
4-4R	93	37	40	350	-----	80
4-5L	96	40	42	350	0.000	80
4-5R	96	38	40	350	-----	80
4-6L	93	39	42	350	0.000	80
4-6R	93	40	43	350	-----	290
6-4	152	50	33	450	-----	290
6-5	152	57	38	450	-----	290
6-6	152	58	38	450	0.000	250
8-7R	145	55	38	700	0.050	250
8-7L	145	50	34	700	0.030	125
16-1L	228	69	30	1700*	0.003	125
16-2L	228	74	32	1700*	0.002	125
16-2L	228	76	33	1700*	0.001	125
16-4L	228	77	34	1700*	0.000	125
16-5L	228	71	31	1700*	0.000	125

* Uterine circulation perfused by pumping the CO-dextran-Krebs solution into a catheter placed in the maternal abdominal aorta rather than into the femoral arteries.

from the pregnant horn. Serial samples from the uterine vein in the non-pregnant horn gave values of 46%, 44%, 47%, 45% and 46% (mean 45·6%) for the maternal shunt. Figure 13 shows the values for the maternal and fetal shunt given in tables 13 and 14 plotted with the N_2O, C_2H_2 points given in appendix 2.

Fig. 13. $T^{M}T^{F}$ plot of the means of the 85 N_2O and C_2H_2 data pairs that are less than 0·1 scale units apart obtained by perfusing 23 near term goat placentas at various ratios of umbilical to uterine blood flow, together with the means ($\pm$ two standard deviations) of the carbon monoxide data for the maternal side (ordinate) and the fetal side (abscissa) obtained by perfusing the goat uterus and placenta respectively with CO - dextran - Krebs solution.


10
5.0
3.0
2.0
1.5
← R^M →
1.0
T^M
↑ R^M ↓
0.8
0.6
0.4
0.2
Mean values for C2H2 and N2O
Mean values ± 2 SD for CO shunts
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0
0

DISCUSSION

A. THE HEMODYNAMIC AND RESPIRATORY GAS STATUS OF PERFUSED PLACENTA

The placenta or the pregnant uterus have been artificially perfused by several workers (3, 18, 20, 23, 28, 59, 62, 65, 67). The usefulness of the inferences drawn after the extrapolation of information gained from the perfusion of the uterus or placenta, to the intact animal depends on the nature of the information itself. No placental perfusion in the sheep has ever been shown to operate at physiological flows and pressures. Alexander et al. (3) perfused the near term sheep placenta with plasma at flows of about 100 ml./min. and Metcalfe et al. (59) obtained similar flows with a dextran - saline perfusate. These umbilical flow rates are considerably lower than the 400 to 500 ml./min. that are observed in the intact preparation (57). Campbell et al. (20) and Nixon (65) perfused the placentas of near term sheep with blood and only obtained 25% of the normal umbilical flow. The only placental perfusion that has been reported to function at physiologically normal flows and pressures is that of Faber and Hart (28) who perfused rabbit placentas with freshly drawn rabbit blood. The success of this preparation may, in part, be ascribed to the filtering of the inflowing blood.

The placental perfusions performed in the experiment

described in the previous chapters did not achieve normal flows at normal pressures. At an umbilical arterial pressure of 55 mm. Hg, the average umbilical blood flow was about 150 ml./min. x kg. fetus which is much greater than the flows reported by Campbell et al. (20) or Nixon (65) but less than the value of 233 ml./min. x kg. fetus reported in the intact animal by Meschia et al. (57). The increased resistance seen in our preparation was probably due to vascular spasm or to the blocking of some vessels by microemboli.

Huggett (43) considers that the time during which the umbilical vessels are occluded during catheterization is critical. In our preparation, the whole cord was never occluded but each vessel was occluded individually and catheterized within 1 minute of the initiation of the occlusion. Huggett (43) considers 4 minutes to be the maximum time that a vessel can be occluded without serious vasospasm.

While some degree of vasospasm probably played a role in increasing the resistance of the placentas, the blocking of small vessels with microemboli may have been a more significant factor. The filters used by Faber and Hart (28) were designed for flows up to 10 ml./min. whereas the filters used in the perfusion of the goat placenta had to be designed for flows up to 500 ml./min. The pressures required to force blood through a filter are determined

by the diameter, thickness and density of the filter. Two 6 inch diameter circular filters were used in parallel during the perfusion of the goat placenta giving a total cross section of 72 square inches. Even with this large surface area the thickness of the cotton wool filtering agent was limited to 0·25 inches which was much less than that used by Faber and Hart. The use of thicker filters caused breaks in the input line due to the high pressures required to maintain the flow of blood through the filters. It is probable that microemboli developed in the blood used in the perfusion circuit during the overnight storage period. The filters may not have been thick enough to remove those clots and if this were the case, the placenta itself would have acted as a filter during the first passage of the blood through this organ. After all of the blood in the perfusion circuit had passed through the placenta once, the microemboli would have been removed and no further increase in resistance would be expected. At a flow of 200 ml./min, which was normal during the post-cannulation period, this initial increase in placental resistance would have occurred within 15 minutes. During this time the uterus was being replaced in the abdomen and the goat was being lowered deeper into the bath preparatory to commencing the first equilibration period. The manipulations necessary to the performance of these preliminary tasks produced pressure fluctuations which masked

any slow increase in umbilical arterial pressure. After the first 15 minutes of perfusion the resistance of the placenta did not change greatly over a period of one to two hours indicating that there may have been little further formation of clots that the filters could not remove.

A third possible reason for the difference between the pressure flow characteristics of the placentas used in these experiments and those thought to exist in the intact animal is the respiratory gas status of the inflowing blood. Panigel states that "for a satisfactory maintenance of the perfused placenta or umbilical cord the normal ratio of dissolved respiratory gases in the physiological fluids must be maintained throughout the experiment" (67). Panigel showed that a higher P_{O_2} than normal caused the arteries of the human cord to contract slowly and even to occlude. He also showed that a high umbilical arterial P_{CO_2} produced a vasodilation. For this reason, during our placental perfusion the P_{O_2} and P_{CO_2} of the perfusing blood was kept as close as possible to the P_{O_2} and P_{CO_2} found in the intact fetus; Table 8 of the previous chapter indicates the measure of success that was achieved. It should be noted that Faber and Hart (28) used an umbilical arterial P_{O_2} of zero for their perfusions of the rabbit placenta. If Panigel (67) is correct, this procedure may have induced some degree of vasodilation which may have contributed in part to the relatively low

placental resistance.

Having established that the goat placentas in our study had a higher resistance than normal and that this may have been due to vasospasm and vessel blockage it remains to show how this may affect the results. The primary aim of the study was to obtain sufficient data to make a $T^{M}_{T}{}^{F}$ plot of the exchanging characteristics of the goat placenta. It should be noted that the calculation of T^{M} and T^{F} is dependent on the ratio, not the absolute magnitude, of the umbilical and uterine blood flows. Providing the orientation and permeability of the exchanging vessels and the distribution of the flows within the utero-placental tissue is not affected, the $T^{M}_{T}{}^{F}$ point representing the transfer of an infinitely diffusible substance across a placenta will be the same at umbilical and uterine flows of 100 and 200 ml./min. respectively as it will at 1000 and 2000 ml./min. respectively. It seems unlikely that vessel orientation and permeability could be affected by vasospasm and vessel blockage, so that the only consideration necessary for the extrapolation of our conclusions to the intact animal are those relating to the distribution of the blood flows within the utero-placental tissue. The effects of vessel blockage on this distribution will be considered during the discussion of shunts and the effect of vasospasm and abnormal arterial P_{O_2} and P_{CO_2} will be considered during the discussion of the uneven dis-

tribution of flow to the exchanging area.

B. DATA EVALUATION

In chapter 3, it was stated that 29% of the N_2O and C_2H_2 data were rejected because the $T^M T^F$ points for N_2O were too far away from the $T^M T^F$ points for C_2H_2. At that time it was stated that if the distance (X) between these 2 points exceeded a value of 0·1 the datum was rejected. The possible reasons for discrepancies between the $T^M T^F$ points for N_2O and those for C_2H_2 will be discussed in this section.

1. Analytical error can cause such a discrepancy, especially as the equations for T^M and T^F are ill-conditioned. That is to say, small errors in individual analyses can result in large errors in T^M and T^F. An example of this effect would be the case where the true value of T^M is given by the relationship (100 - 90) / (100 - 0) which equals 0·1. Such an example could be obtained from N_2O analyses. If the standard deviation of the analytical technique were 2%, a range of 2 standard deviations on each side of the mean would permit the figure of 100 to be between 96 and 104. The figure of 90 would range from 86·4 to 93·6. The value of T^M could therefore range from 0·169 to 0·025 in extreme cases. This range is from 25% to 169% of the true value for T^M even though the standard deviation of the analytical technique was 2%.

The standard deviation of the gas chromatographic analyses

varied from 1% to 2% for duplicate determinations depending on the height of the readout peaks. Peaks which were drawn by large deflections of the recorder could be more accurately estimated than lower peaks because it is easier to discriminate 1% of a peak that occupies 90% of the full scale deflection than 1% of a peak that occupies 20% of the full scale deflection. It can be seen that the error in T^M and T^F, introduced by errors in the analysis, would be smallest where the arterio-venous differences are largest, and greatest where the arterio-venous differences are smallest. For this reason the values of T^M would be affected most at low flow ratios and values of T^F would be affected most at the higher flow ratios. There is no reason to expect that the analytical error would impose a significant bias on the $T^M T^F$ values, because the denominator of the equations for T^M and T^F is the uterine to umbilical arterial concentration difference, the figure least affected by the error due to condition. The analytical error would have its main effect in the numerators of these equations so that the analytical errors introduced into T^M and T^F would have an essentially Gaussian distribution.

2. Leakage of gas from the uterine or fetal placental tissue would cause the $T^M T^F$ points for N_2O to be different from those for C_2H_2. If N_2O was being lost through the uterine surface it would probably be coming from the myometrial blood flow which

is considered to be part of the maternal shunt. This loss would cause the shunted blood on the maternal side to enter the venous outflow with a concentration of N_2O that was less than that of the maternal artery. Consequently the amount of N_2O in the maternal venous sample would be less than expected and $T^M_{C_2H_2}$ would be less than $T^M_{N_2O}$. A similar argument applies to the situation arising from the loss of C_2H_2 from the free surface of the fetal placenta in which case $T^F_{C_2H_2}$ would be greater than $T^F_{N_2O}$.

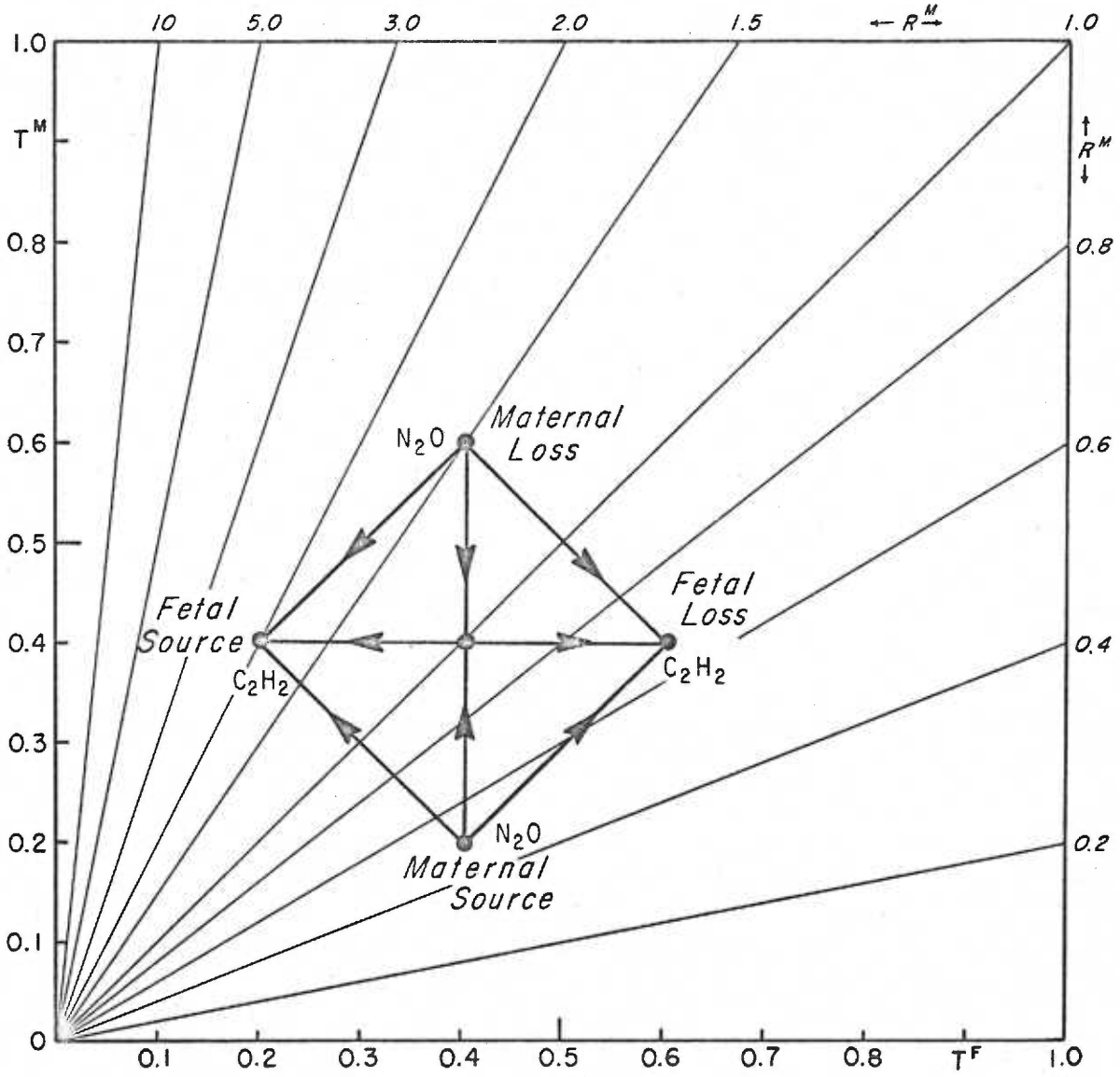
3. Changes in the concentration of C_2H_2 and N_2O in the umbilical and uterine arterial blood would produce transient discrepancies between the T^MT^F points for N_2O and C_2H_2. A decrease in the amount of N_2O in the uterine arterial inflow would not be immediately apparent in the venous outflow from the maternal shunt. The amount of N_2O in the uterine tissues would decrease over a period of time and during this period there would appear to be a source of N_2O in the uterine tissue. This would cause the $T^M_{N_2O}$ to be less than the $T^M_{C_2H_2}$. An increase in the N_2O concentration in the uterine artery would result in the $T^M_{N_2O}$ being greater than $T^M_{C_2H_2}$ for a period of time. Changes in the C_2H_2 content of the umbilical arterial blood would cause equivalent changes in $T^F_{N_2O}$ versus $T^F_{C_2H_2}$.

The effects of gas loss from the fetal or maternal side and changes in arterial gas concentrations are shown in Figure 14.

Fig. 14. The effect of gas losses and gas sources in the uterine (maternal) and umbilical (fetal) circulation on the $T^{M}{}_{T}{}^{F}$ points for N_2O and C_2H_2. The arrows run from the N_2O point to the C_2H_2 point.

Gas losses would occur if N_2O was leaking from the surface of the uterus or C_2H_2 was leaking into the allantoic space. Apparent gas losses would occur if the concentration of N_2O in the uterine arterial flow or C_2H_2 in the umbilical arterial flow, suddendly increased.

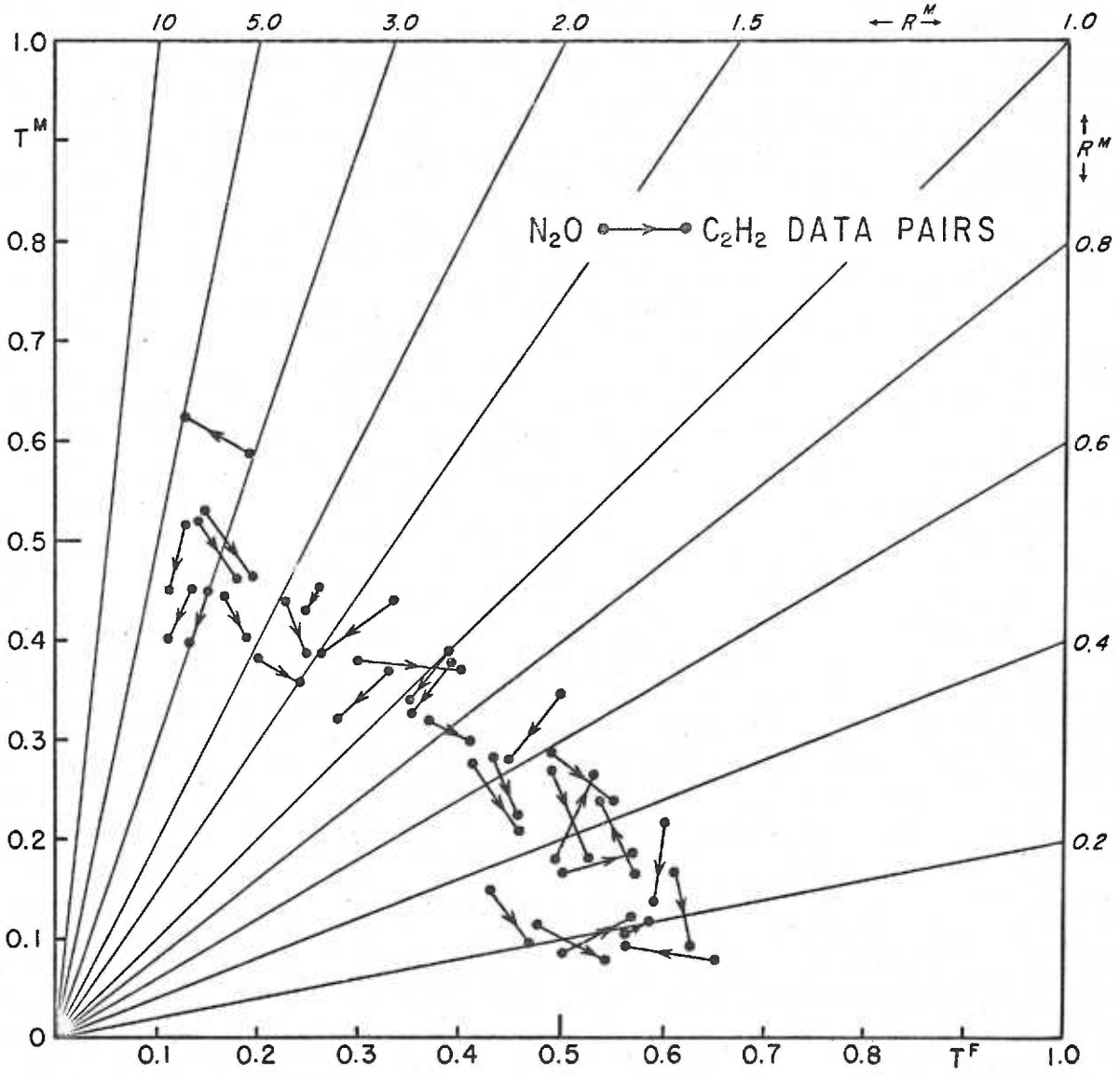
Apparent sources of gas would occur if the concentration of N_2O in the uterine arterial flow or the concentration of C_2H_2 in the umbilical arterial flow suddenly decreased.


10
5.0
3.0
2.0
1.5
← R^M →
1.0
1.0
T^M
↑ R^M ↓
0.8
0.8
0.7
0.6
0.6
0.5
0.4
0.4
0.3
0.2
0.2
0.1
0
N2O
Maternal Loss
Fetal Source
Fetal Loss
C2H2
C2H2
N2O
Maternal Source
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0

The criterion for the rejection of data would remove data invalidated by analytical error, loss of gas from the shunted flows and changes in arterial gas content. Figure 15 shows several N_2O and C_2H_2 points that were acceptable. It was not possible to plot all of the acceptable data pairs in this way because the representation becomes confusing. The data pairs shown in Figure 15 are a representative sample selected to show the general relationship between the N_2O and C_2H_2 points over a range of flow ratios. Data pairs that were close together are not shown.

If either N_2O or C_2H_2 were not infinitely diffusible the T^MT^F points for these 2 gases would be separate. Figure 15 shows that the C_2H_2 points tend to be closer to the origin than the N_2O points. If this were due to a permeability difference between the two gases it would indicate that C_2H_2 was less diffusible than N_2O. Faber and Hart (28) show that the transfer of C_2H_2 is not limited by diffusion in the rabbit placenta. These authors also showed that the d^M value for tritiated water was between 1·8 and 4·0 under the conditions of their study (29). Meschia et al. (54) showed that the transfer of tritiated water across the sheep placenta was essentially flow limited which implies that $d^M_{N_2O}$ was greater than 10. It would appear from this that the sheep placenta is more permeable to water than the rabbit placenta. As the transfer of C_2H_2 in the rabbit placenta is not limited by diffusion, it

Fig. 15. $T^{M}T^{F}$ plot of 31 of the more widely separated acceptable N_2O and C_2H_2 data pairs. The arrow runs from the N_2O point to the C_2H_2 point. The data pairs are a representative sample selected over the full range of flow ratios to illustrate the relative positions of the N_2O and C_2H_2 points.


10
5.0
3.0
2.0
1.5
← R^M →
1.0
1.0
T^M
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
↑ R^M ↓
0.8
0.6
0.4
0.2
N2O → C2H2 DATA PAIRS
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0

seems reasonable to assume that the transfer of C_2H_2 in the sheep placenta, and by extrapolation, the goat placenta is not limited by diffusion either. This would mean that any separation of the T^MT^F coordinates for N_2O and C_2H_2 due to differences in permeability of these gases must result in the N_2O point being closer to the origin than the C_2H_2 point. It therefore seems unlikely that the placental transfer of N_2O and C_2H_2 is limited by diffusion and that the separation of the T^MT^F points for these gases, as shown in Figure 15 is due to other causes.

Three further variables which would result in T^MT^F coordinates not comparable with the predicted behavior of model placentas are changes in placental permeability, effectiveness, and blood flow. Each of these variables change the T^MT^F coordinates for N_2O and C_2H_2 in the same way so that the N_2O and C_2H_2 points do not separate during transient changes in these variables. The rejection criterion does not select T^MT^F points that are affected by these changes. It should be pointed out that it is unlikely that the permeability of the placenta would change spontaneously. The work of Power and Longo (71) indicates that the distribution of the umbilical and uterine flows is capable of changing and the effectiveness of the placenta would change as a result. It is unlikely, however, that there were spontaneous changes in the arterial P_{O_2}'s of sufficient magnitude to cause

significant changes in effectiveness.

The most serious source of error not detected by the criterion of distance between the N_2O and C_2H_2 data pairs would be variable uterine blood flows. It is quite probable that this flow did change during the 30 minute equilibration period but it should be noted that in response to a change in this flow the $T^{M}T^{F}$ points would move to the locus of the new flow ratio together and in a straight line because the time course of the change in N_2O and C_2H_2 concentrations in the umbilical veins were found to be the same as those in uterine veins. This means that a $T^{M}T^{F}$ point obtained during such a transient period would be on the wrong R^{M} line but would not leviate much from the normal $T^{M}T^{F}$ line along which that particular exchanger operates. The effects of transient changes in flow would not therefore invalidate the comparison of data obtained from an experimental preparation to the $T^{M}T^{F}$ line representing the predicted behavior of a model exchanger.

C. SHUNTS

A shunt has been defined as that fraction of the uterine or umbilical blood flow that does not participate in transplacental exchange. The representation of the exchanging characteristics of the placenta on a $T^{M}T^{F}$ diagram has been shown to be particularly useful, in that the value of T^{M} at a flow ratio (R^{M}) of infinity is equal to $1 - S_M$, where S_M is the maternal shunt, and the value of

T^F at a flow ratio (R^M) of zero is equal to 1 - S_F, where S_F is the fetal shunt.

It can be seen that the shunts can be evaluated by extrapolating the line, represented by the N_2O, C_2H_2 data, to the axes of the T^MT^F plot and by using the CO technique of Metcalfe et al. (59). This latter technique depends on the fact that hemoglobin binds CO, so that if one side of the placenta was perfused with a solution containing CO and no hemoglobin and the other side was perfused with a solution containing hemoglobin and no CO, then the hemoglobin containing flow would appear to be infinitely larger than the CO containing flow. In this way a CO - dextran - Krebs solution perfused into the umbilical arteries would cause the preparation to appear to have a flow ratio (R^M) of zero. If such a solution was perfused into the uterine arteries, the preparation would appear to have a flow ratio of infinity.

Figure 13 shows that with blood perfusion it was not possible to obtain flow ratios close to the axes of the T^MT^F plot. This renders the extrapolation of the N_2O, C_2H_2 data to the axes somewhat indefinite especially as the data are more scattered at the extreme flow ratios. A further problem with the extrapolation is that the T^MT^F plot of a realistic model is rarely, if ever, a straight line. The extrapolation to the axes would therefore have to be along a curve, which renders the intercepts of the extrapolation

with the axes even more indefinite. The CO shunts are within the range of values that would be compatible with an extrapolation of the N_2O, C_2H_2, data points of Figure 13, to the axes and occupy a smaller range than does the extrapolation of the band of N_2O, C_2H_2 points to the axes. It would therefore be preferable to define the shunts with the CO data and the shape of the T^MT^F line along which the goat placenta operates, with the N_2O, C_2H_2 points. Before this can be done some of the assumptions necessary to the CO technique must be discussed.

1. The CO technique assumes that all of the CO is removed from the dextran - Krebs solution during one pass through an exchanging capillary. The corollary to this assumption is that all of the CO detected in the venous outflow comes from shunted perfusate. If the assumption was invalid and some CO remained in the perfusate after traversing the exchanging capillaries then the venous CO concentration would be excessively high. This would result in a calculated shunt that was larger than the true value. There are two pieces of evidence to indicate that this does not happen and that all of the CO is stripped from the exchanging flow. Firstly, the CO shunts are not higher than those given by the extrapolated band of N_2O, C_2H_2, points. If anything, the CO shunts are a little lower than may be expected from the extrapolation. Secondly, if the exchanging flow was not stripped of all its CO, there would be

an end capillary CO gradient across the exchanging area. If the flow was then increased, the end capillary CO gradient would be increased. The shunt, as calculated from the CO would then be dependent on the flow of perfusate. Table 14 shows that even though the flow of CO - dextran - Krebs solution used to measure the maternal shunt ranged from 200 ml./min. to 1700 ml./min., the value of the maternal shunt did not change. These flows were not uterine flows but it is unlikely that the uterine flow remained constant in the face of such wide variation in femoral or aortic flow. These arguments suggest that the CO was essentially removed from the perfusate that passed through the exchanging capillaries.

2. The CO technique assumes that the CO - dextran - Krebs perfusate contains no hemoblogin, so that the CO is present in physical solution only and is free to diffuse across to the blood on the other side of the exchanging area. This assumption is certainly valid as applied to the fluid entering the arterial catheters but is not valid as applied to the fluid in the venous outflow. Table 14 shows that the maternal venous outflow contained up to 0.03 gm.% of hemoglobin during determinations of the maternal shunt. There was little or no hemoglobin in the umbilical venous outflow during determinations of the fetal shunt.

The presence of hemoglobin in the venous outflow does not

automatically invalidate the technique. If the hemoglobin was added to the perfusate after it had passed through the exchanging capillaries it would not interfere with the movement of CO across the exchanging area. If, however, the hemoglobin was added before the perfusate cleared the exchanging capillaries it would take some CO out of solution and prevent the complete transfer of CO to the blood on the other side of the exchanging area. Had this been the case during the determination of the maternal shunt, the shunt values would have been dependent on the amount of hemoglobin present, the more hemoglobin present the greater the apparent shunt. It can be seen from table 14 that even though the hemoglobin in the uterine venous outflow ranged from 0 to 0·03 gm. %, the values for the maternal shunt did not change. This permits the conclusion that the hemoglobin was added after the perfusate traversed the exchanging capillaries and did not affect the calculation of the maternal shunt because 0·03 gm. % of hemoglobin added on the arterial side would have been sufficient to increase the shunt value by up to 5 to 10%. The hemoglobin was probably added to the perfusate during its passage through the uterine veins and may have reflected a slower purging of these vessels due to the relatively low velocity of venous flow.

The remaining three assumptions are relevant to the estimate of the shunts provided by the N_2O, C_2H_2 data as well as the

CO data.

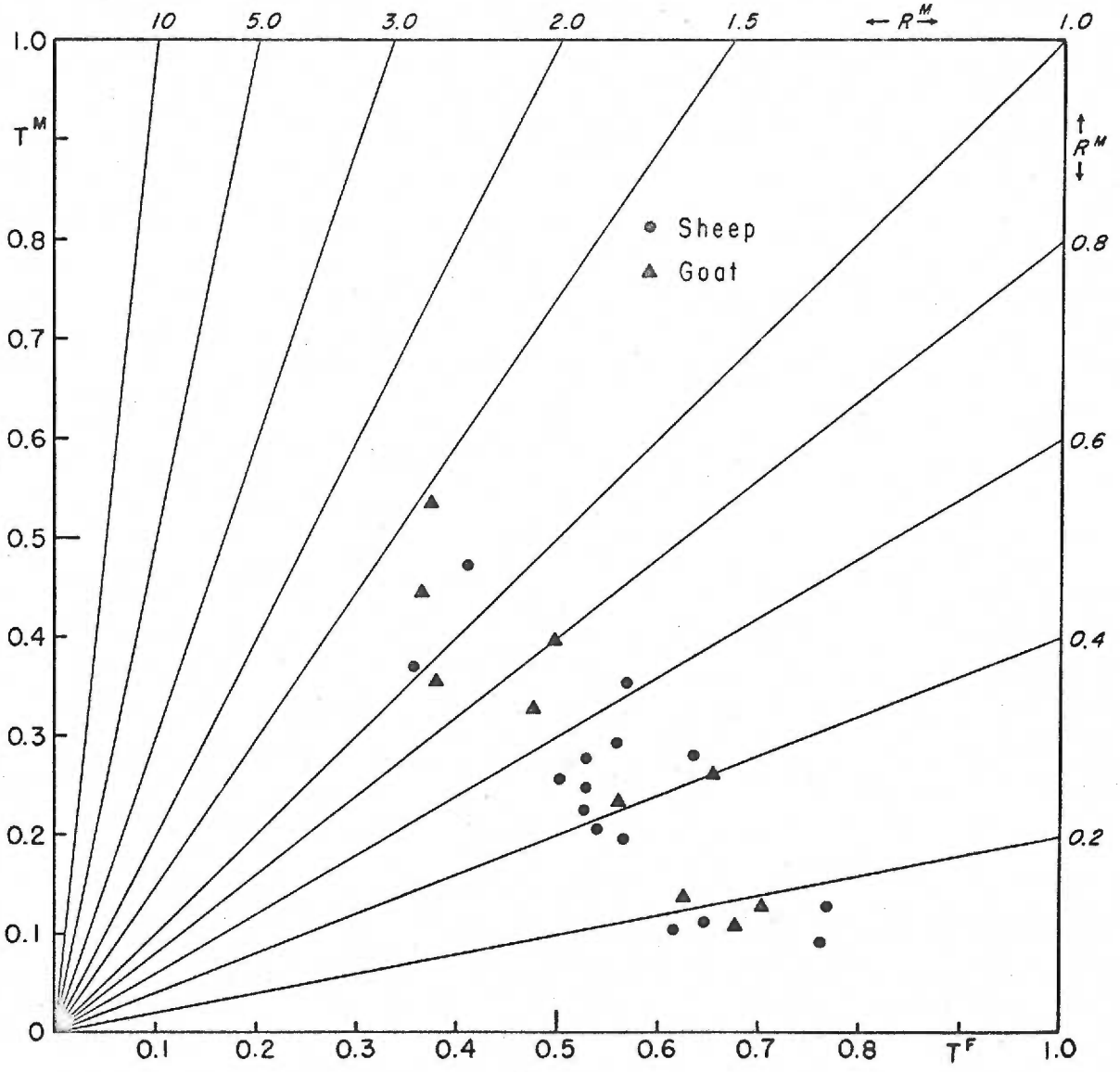
3. It is assumed that the venous blood samples are representative of the whole venous outflow. This assumption is certainly valid as applied to the fetal side of the placenta because the blood samples were taken directly from the umbilical venous outflow which was channeled into a single tube in the perfusion circuit. The representative nature of the uterine venous samples cannot be so easily defended. The uterine venous catheter was threaded into a superficial vein which was more likely to be draining the myometrium than the exchanging area. The catheter was advanced until its tip was thought to be in a common uterine vein at the approximate level of the ovaries. If the catheter was advanced too far it would sample blood from the inferior vena cava. If it was not advanced far enough it would sample blood from adjacent myometrial veins. Each of the above conditions would result in samples that appeared to be drawn from an exchanger with an excessively large maternal shunt.

It is difficult to conceive of a mechanism whereby a catheter threaded into a myometrial vein could give samples that would result in the calculation of an erroneously small maternal shunt. This situation could only happen if the catheter were bent back upon itself and the tip advanced in a retrograde fashion into a vein draining the exchanging area. The post-mortem inspection was specific-

ally oriented to the detection of this type of error and on no occasion was the catheter seen to have reversed its direction in such a manner.

Errors in the placement of the uterine venous catheters can therefore primarily increase the apparent maternal shunt. This error would be expected to occur as frequently in the perfusions using N_2O and C_2H_2 as in those using CO. The fact that there is very little variation in the maternal shunt, as calculated from CO, indicates that the placement of the uterine venous catheter was consistent. It may well have been consistently wrong however, and the possibility remains that the maternal shunt is erroneously high in all of the experiments. This possibility is suggested by the slope of the line in Figure 16. The data points in Figure 16 were calculated from information given by Meschia et al. (54, 57) on the placental transfer of antipyrene in intact sheep and goats. Figure 16 shows that there is no difference between the $T^M T^F$ plot for the sheep placenta and that for the goat placenta as defined by these data. The projected intercept of the band of antipyrene points with the T^M axis indicates a maternal shunt of between 10% and 30%, although the extrapolation may not be warranted as the available range of flow ratios is small. It therefore appears that the estimates of the maternal shunt obtained from data supplied by Meschia's group are lower than those obtained by placental perfusion which would be

Fig. 16. $T^{M}T^{F}$ plot of the placental transfer of antipyrene in intact near term sheep and goats calculated from data presented by Meschia et al. (54, 57). The solid circles represent data obtained from sheep. The crosses represent data obtained from goats.


10
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← R^M →
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1.0
T^M
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
↑ R^M ↓
0.8
0.6
0.4
0.2
Sheep
Goat
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0

expected if the placement of the maternal venous catheters was such that they were not drawing representative mixed uterine venous blood or that some of the fetal capillaries were blocked, a point that is considered in the following discussion.

4. It is assumed that none of the fetal capillaries were blocked during the perfusion of the placenta with blood. In the discussion of the hemodynamic status of the preparation it was pointed out that the pressure - flow characteristics of the preparation indicated that there was some degree of vasospasm or vessel blockage present in the umbilical circulation. It should be realized that if any of the exchanging vessels on the fetal side were blocked then the adjacent uterine vessels would deliver shunted blood to the uterine veins whereas in the normal state they would have delivered blood from an exchanging area. This would cause the maternal shunt seen in the perfused preparation to be larger than normal.

The effects of unrepresentative uterine venous blood samples and blocked umbilical blood vessels would affect both the CO data and the N_2O, C_2H_2 data to some degree. The fact that the N_2O, C_2H_2 data are compatible with the CO data and that data from each of these sources indicates a larger maternal shunt than does the data of Meschia et al. (54, 57) suggest that the maternal shunt in the perfused placenta is larger than normal. It should be

realized that these arguments do not invalidate the estimates of the fetal shunt. The dimension of the fetal shunt obtained from the N_2O, C_2H_2 data for the goat placenta, the CO data for the goat placenta and the sheep placenta (59) and the antipyrene data for the goat and sheep placenta (54, 57) all give the same value of approximately 20%.

5. The CO technique requires that one further assumption be made. That the distribution of the CO - dextran - Krebs perfusate between the shunting and exchanging pathways is the same as that of blood in the intact uterine and perfused umbilical circulations. It may be expected that the tissues served by the shunted flows would become relatively more anoxic during CO - dextran - Krebs solution perfusion than the tissue adjacent to the exchanging area because the latter tissues could obtain oxygen by the diffusion of that gas from the blood flowing on the other side of the exchanging area. This could be postulated to result in a vasodilation of the shunting pathways with a consequently increased fraction of the flow being shunted than would otherwise be the case. If such an error occurred it would affect the CO determination only. The N_2O, C_2H_2 data would then be representative of an exchanger with less shunting than the CO data. Figure 13 shows that this was not the case, that the CO data and N_2O, C_2H_2 data do not appear to be obtained from an exchanger with different degrees of shunting, and that the CO - dextran - Krebs solution was distributed

between the shunting and exchanging pathways in the same proportions as the uterine and umbilical blood flows.

In summary, the CO technique appears to be a useful procedure for the determination of the maternal and fetal shunts. Shunts determined in this manner provide a reasonably accurate, repeatable estimate of the intercepts of the $T^{M}_{T}{}^{F}$ line representing the exchanging characteristics of the placenta in question but the perfusion of the umbilical circulation and the placement of the uterine venous catheters may have resulted in a larger maternal shunt than that of the intact preparation. The erroneously large maternal shunt would not affect the comparison of the N_2O, C_2H_2 data obtained from the preparation with the predicted behavior of various placental models provided the $T^{M}_{T}{}^{F}$ line representing the behavior of these models is adjusted for a maternal shunt of 36% and a fetal shunt of 23% as found in the perfused goat placenta.

D. COMPARISON WITH VARIOUS MODELS

It has been established that the $T^{M}_{T}{}^{F}$ plot of the N_2O and C_2H_2 data represents the pattern of exchange in the goat placenta with a maternal shunt of 36% and a fetal shunt of 23%. It has further been explained that the degree of diffusion limitation of N_2O and C_2H_2 is very probably close to zero. These two items of information permit the exchanging characteristics of a model placenta to be compared to those observed during the perfusion of the

goat placenta. To make this comparison the $T^M T^F$ values for the d^M = infinity line of a particular model are adjusted for the shunts by multiplying all values of T^M by 0·64 and all values of T^F by 0·77. The resultant line represents the exchange of an infinitely diffusible substance in an exchanger of that particular type with those particular shunts.

The most convenient models to work with are the concurrent and countercurrent types. It is not necessary to deal separately with a crosscurrent model because when d^M = infinity, Ntu = infinity. Tables 3 and 4 show that in this case the exchanging characteristics of the countercurrent exchanger are identical to those of the crosscurrent exchanger. The particular case of a crosscurrent exchanger with one flow mixed may be more relevant to the primate placenta which has a multivillous pool, than to the goat placenta.

In a recent abstract, Faber (27) demonstrated the effects of unevenly distributed flows on the transfer of an infinitely diffusible substance in concurrent and countercurrent exchangers. These graphs have not as yet appeared in the literature but have been made available for the purposes of this discussion. Faber considered three cases:

a. Evenly distributed flows

b. Moderately uneven distribution

c. An extremely uneven distribution

These graphs have been adjusted for the shunt values found in the goat placenta by the CO technique of Metcalfe et al. (59) and are presented together with the N_2O, C_2H_2 data in Figure 17. Faber calculated the T^MT^F coordinates of the two types of exchangers with unevenly distributed flows by dividing each exchanger into 5 equal sections. The flows were distributed to each of these sections in the following way:

Moderately uneven distribution

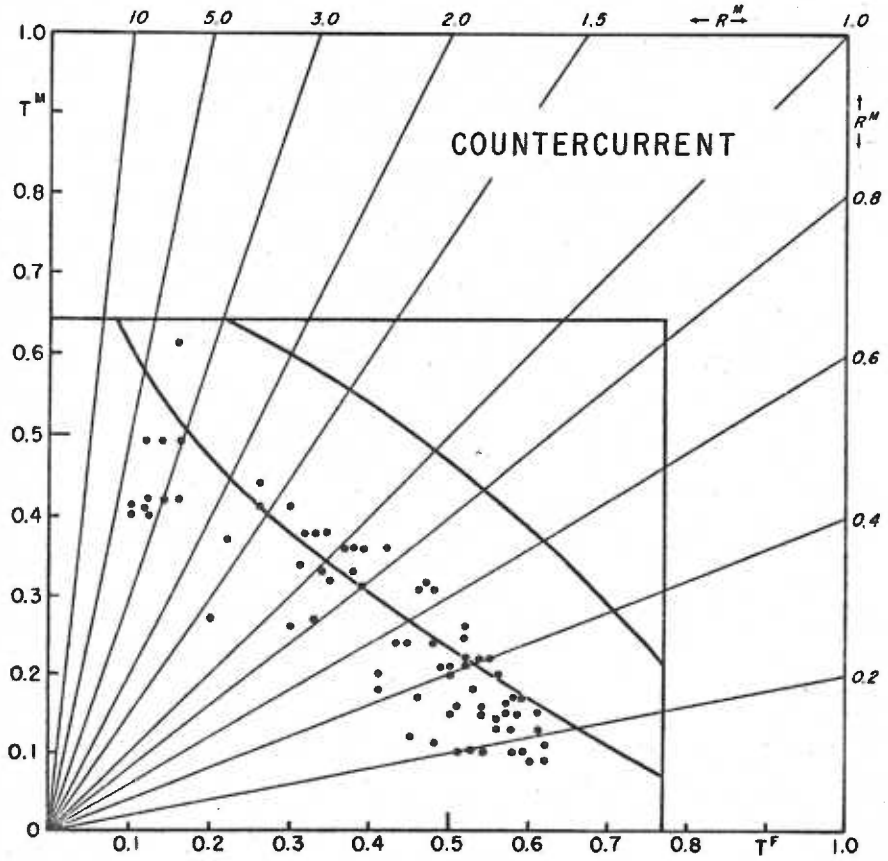
R^M or R^F = 9/3 3/5 1/1 5/3 3/1

Extremely uneven distribution

R^M or R^F = 1/9 3/7 1/1 7/3 9/1

The 5 sections were then treated as separate placentas in parallel. The concentration of exchanging substance in the mixed venous outflow was calculated at various flow ratios in both concurrent and countercurrent models. The T^MT^F coordinates could then be calculated and plotted. Faber (27) used a computer to perform these manipulations but a numerical example is presented in appendix 6 to demonstrate the details of the method. Figure 17 shows that the goat placenta has the exchanging characteristics of a countercurrent model with an extremely uneven distribution of blood flow or a concurrent model with quite an even distribution of blood flow. It

Fig. 17. $T^{M}T^{F}$ plot of the transfer of an infinitely diffusible substance in ideal countercurrent and concurrent exchangers with 36% shunted flow on the maternal side and 23% shunted flow on the fetal side. The 3 lines on each plot represent, from the top, the effects of evenly and moderately and extremely unevenly distributed flow ratios. (Taken from Faber (27)). Superimposed on this plot are the mean $T^{M}T^{F}$ points for N_2O and C_2H_2 data pairs less than 0·1 scale units apart.


COUNTERCURRENT
10
5.0
3.0
2.0
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← R^M →
1.0
T^M
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0.8
0.6
0.4
0.2
0
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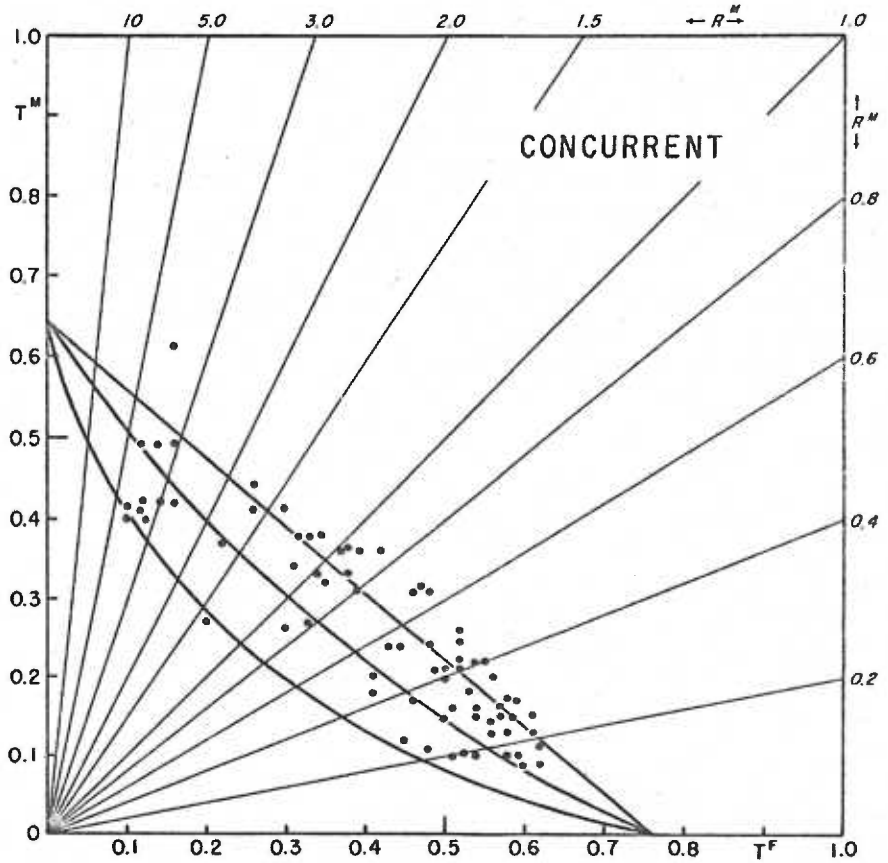
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0


CONCURRENT
10
5.0
3.0
2.0
1.5
← R^M →
1.0
T^M
↑ R^M ↓
0.8
0.6
0.4
0.2
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0

It can be seen that the further definition of the exchanging characteristics of the goat placenta requires additional information pertaining to the distribution of the blood flows over the exchanging surfaces.

Recently Power et al. (71) have described a technique which permitted them to measure the distribution of blood flows in the sheep placenta. In view of the demonstrated anatomical and physiological similarity between the placentas of these two species, especially as shown in Figure 16, the application of the data of Power et al. to the goat placenta seems to be justified. Unfortunately these authors only provide detailed information on one animal, sheep # 15. The relevant information is a plot of per cent placental weight versus the ratio of the relative activity of I^{125} on the maternal side of the placenta to the relative activity of I^{131} on the fetal side of the placenta. It will be remembered that the activities of I^{125} and I^{131} were used as a measure of flow distribution. Details of the calculation of the $T^{M}_{T^{F}}$ lines for a concurrent and countercurrent exchanger with the flow distribution shown by Power et al. are given in appendix 6. When divided into 5 sections the placenta of sheep # 15 had the maternal and fetal flows distributed as follows:

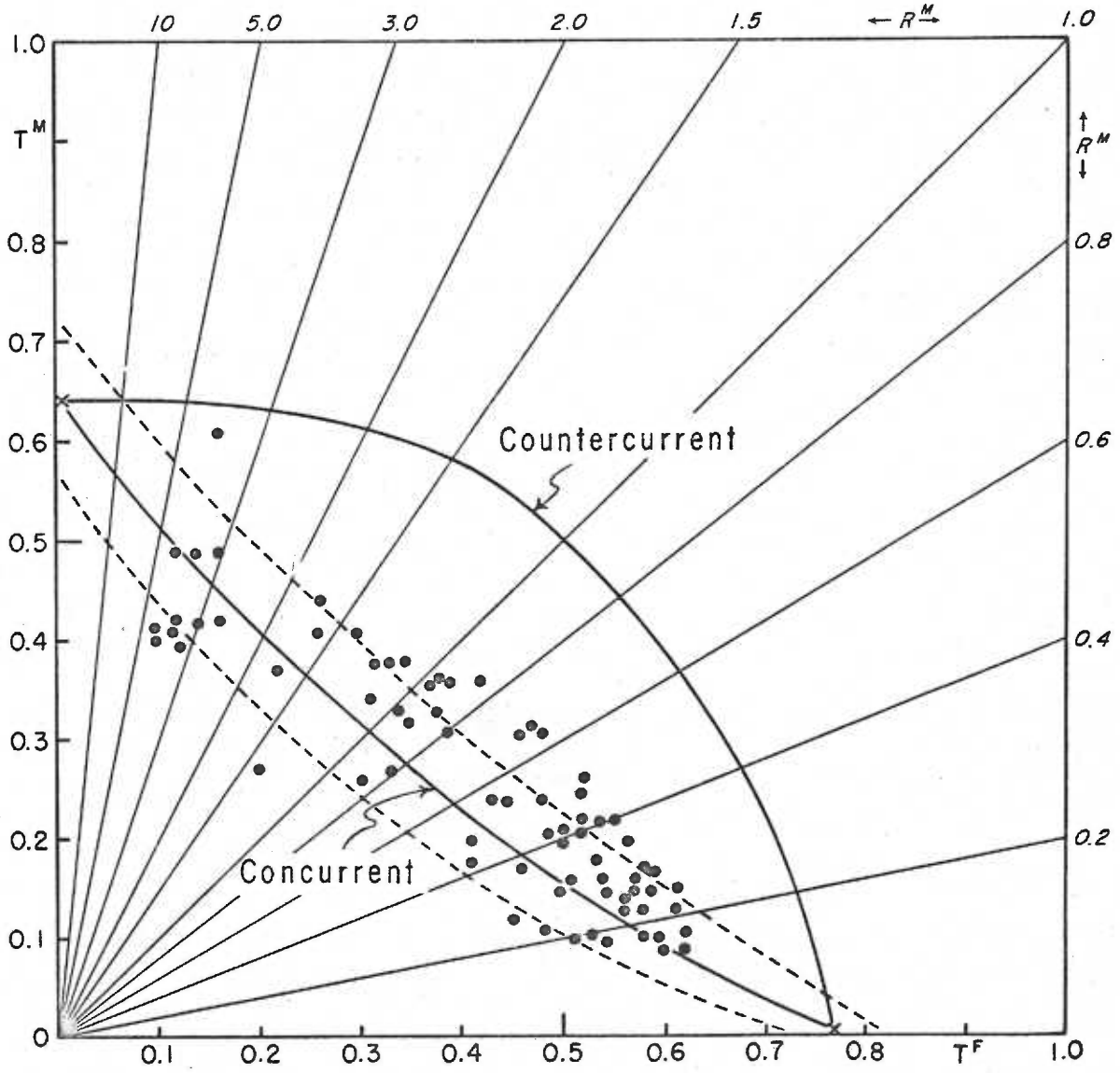
Maternal to fetal flow ratio

.242 .456 .726 1.318 2.165

It can be seen that the ratio (R^F) ranges from .242 to 2.165, a 9 fold range, the same as the 1/3 to 3/1 distribution that Faber (27) referred to as moderate. The $T^M T^F$ plot of a concurrent and countercurrent exchanger each with shunts of 36% and 23% and the flow distribution found by Power et al. is shown in Figure 18 superimposed on the N_2O, C_2H_2 data obtained during the perfusion of the goat placenta at various flow ratios.

It can be seen that if the data of Power et al. (71) is correct then the goat placenta behaves as if it were a concurrent exchanger. This conclusion is at variance with the anatomical findings of Barcroft and Barron (8) and with Steven's interpretation (78) of his own anatomical findings which indicate that this type of placenta resembles a countercurrent or crosscurrent model. To be either of these types the distribution of flows would have to be more uneven than Power et al. (71) report by one order of magnitude. It is difficult to evaluate the accuracy of the distributions of flows reported by Power et al. but it is unlikely that they would be in error by a factor of 10. On the other hand, the anatomical evidence is at variance within itself and, in our opinion, an inspection of Steven's (78) illustration in Figure 3 indicates that large segments of the sheep placenta could indeed function as concurrent exchangers. If the anatomical description of this type of placenta is so difficult as to cause a disagreement among the

Fig. 18. The $T^{M}T^{F}$ plot of a countercurrent and a concurrent placenta with the flow distribution specified by Power et al. (71) adjusted for a maternal shunt of 36% and a fetal shunt of 23%. The dotted lines represent the concurrent model with shunts differing from the mean of the CO data by 2 standard deviations on either side. Superimposed on this plot are the mean $T^{M}T^{F}$ points for N_2O and C_2H_2 data pairs less than 0·1 scale units apart.


10
5.0
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← R^M →
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T^M
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0.2
0.2
0.1
0
Countercurrent
Concurrent
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
T^F
1.0

anatomists themselves it may be more logical to accept the physiological evidence which is consistent within itself.

Such a course leads to the conclusion that the goat placenta, while being perfused with blood from the fetal side, has a maternal shunt of 36%, a fetal shunt of 23% and the exchanging characteristics of a concurrent placenta with fairly evenly distributed flows over the exchanging surfaces or a countercurrent or crosscurrent exchanger with extremely unevenly distributed flows over the exchanging area. These conclusions may be extrapolated in the following way. The only available evidence on the distribution of the flows indicates that the goat placenta resembles a concurrent exchanger. The evidence provided by studies of antipyrene transfer (54, 57) indicates that the maternal shunt in the intact animal may be smaller than that observed in the studies using the perfused placenta. Apart from this there is no apparent reason why the shunts and exchanging characteristics of the goat placenta as studied by perfusion cannot be extrapolated to the intact animal.

SUMMARY AND CONCLUSIONS

A technique is described whereby the fetal side of the placenta of the goat near term can be perfused with blood. The ratio of fetal to maternal blood flow was controlled in the range 0·17 to 4·80. The fractions of the maternal and fetal blood flows that did not enter the exchanging area ("shunts") were determined by perfusion of the uterine and umbilical circulations with CO - dextran - Krebs solution and were found to be 36% (sd 3·9%) and 23% (sd 2·2%) respectively. These values were compatible with the shunt values obtained by graphical extrapolation of the data obtained with N_2O and C_2H_2 during perfusion with blood. The N_2O and C_2H_2 data showed that the goat placenta has the exchanging characteristics of a countercurrent or crosscurrent exchanger with extremely unevenly distributed flows or those of a concurrent exchanger with a moderately uneven distribution of flows. The only available information in the literature on the distribution of flows in this type of placenta indicates that the distribution is moderately uneven and that the exchanging characteristics of the goat placenta resemble those of a concurrent exchanger. This conclusion does not agree with the anatomical evidence. These findings can be extrapolated to the intact animal with confidence except for the values of the maternal shunt which may be larger than normal in the perfused preparation.

APPENDICES

Notes on use of appendices 1-5

Appendices 1-5 are included for the purpose of providing information on each specific flow ratio. The proper use of these appendices should permit the reproduction of any and all of the data contained in this thesis. For example, if a flow ratio (R^M) of 1 is desired. Appendix 3 shows that a flow ratio of .985 was observed to occur when datum number 283 was obtained. This appendix also shows that at this flow ratio the goat placenta operates at $T^M T^F$ coordinates of 0.364, 0.369. The amounts of N_2O and C_2H_2 that were observed in the relevant blood vessels is given in appendix 2. Appendix 1 shows that to repeat this observation the following respiratory gas tensions are required in the arterial inflows and would be seen in the venous outflows.

	P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg	(Hb) gm%
MA	120	7.27	32	10.2
MV	44	7.25	38	
FA	16	7.38	40	
FV	26	7.38	36	9.1

Appendix 4 shows that the measurements were made in the right placenta of the 20th goat, at a $\dot{Q}_F$ of 250 ml./min. and a $\dot{Q}_M$ of 260 ml./min. These flows were obtained with umbilical and uterine arterial pressures of 55 and 50 mm. Hg respectively. Occlusion of the mater-

nal abdominal aorta was necessary to decrease the maternal arterial pressure to 50 mm. Hg. Finally, appendix 5 shows that the 20th goat weighed 40.8 Kg and was at the 120th day of gestation. The right fetus weighed 1361 gms., and the right placenta weighed 595 gms. and had 68 cotyledons. The appendices therefore contain all the relevant information necessary to the description of the conditions under which each measurement was made.

Datum numbers are for the purpose of identification only and do not represent the number of data obtained.

APPENDIX 1

Respiratory Gas Status of Maternal and Fetal Blood Samples

These tables contain measurements of P_{O_2}, pH and P_{CO_2} at 39° C and the hemoblogin concentration for 70 sets of blood samples from a maternal carotid artery (MA), uterine vein (MV), umbilical vein (FV), and umbilical artery. These samples were drawn during the placental perfusions described by the data in appendices 2-5. The blood on the fetal side was from adult goats but had been stored for 24 hours. The samples 3-139 had been stored in ACD buffer and suffered some hemolysis. Samples 157-305 were stored in heparin and suffered no hemolysis. Oxygen content was not measured but can be approximated by estimating the per cent saturation from the nomogram for goat blood of Hellegers et al. (39) and multiplying by the hemoglobin concentration and by 1.34, the Hufner coefficient. This

APPENDIX 1

Datum Number	Maternal (Hb) gm %	Maternal Artery			Maternal Vein			Fetal (Hb) gm %	Fetal Artery			Fetal Vein		
		P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg	P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg		P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg	P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg
3		60	7.21		41	7.22			15	7.09		21	6.99	
7		57	7.20		22	7.24			12	7.03		14	6.94	
13		93	7.35		44	7.26			16	6.88		27	6.90	
15		95	7.39		36	7.30			10	6.84		20	6.96	
17		126	7.36		36	7.26			23	6.80		14	6.80	
21		133	7.35	40	32	7.20	66		14	6.88	75	20	6.89	72
25		164	7.34	40	24	7.38	74		10	7.07	80	6	7.03	86
27		174	7.43	43	45	7.40	48		9	7.06	48	34	7.04	49
29		174	7.43	43	46	7.42	44		9	7.06	48	33	7.04	48
31		148	7.43	43	38	7.39	50		13	6.94	58	28	6.95	52
33		148	7.43	43	37	7.41	47		13	6.94	58	27	6.96	56
35		108	7.37	52	37	7.31	68		7	6.97	36	13	6.94	42
37		108	7.37	52	37	7.33	43		7	6.97	36	11	6.95	43
39	10.7	96	7.40	30	40	7.35	37	9.6	19	7.11	36	24	7.02	45
41	↓	96	7.40	29	15	7.08	36	↓	32	7.35	37	25	7.03	45
45	9.5	60	7.30	27	46	7.22	40	9.5	60	6.8	100	52	6.99	51
47	|	60	7.30	27	50	7.18	45	|	60	6.8	100	52	7.15	54
65	|	60	7.30	28	46	7.3	28	|	28	7.14	28	36	7.09	28
67	↓	60	7.30	28	41	7.26	26	↓	28	7.14	28	36	7.11	24
73	10.3	182	7.48		31	7.42		8.6	10	7.09		19	7.05	
77	↓	194	7.44		35	7.37		↓	8	7.01		22	6.97	
85	9.7	206	7.37		55	7.63		8.1	15	7.04		45	7.29	
87	|	206	7.37		46	7.67		|	15	7.04		44	7.05	
89	|	204	7.42		50	7.37		|	22	7.06		37	7.04	
91	|	204	7.42		51	7.38		|	22	7.06		40	7.03	
93	|	198	7.47		37	7.35		|	18	6.98		31	7.00	
95	↓	198	7.47		36	7.35		↓	18	6.98		36	6.98	
97	10.8	59	7.38		45	7.33		9.4	4	6.97		26	6.93	
99	|	59	7.38		43	7.39		|	4	6.97		26	6.95	
101	|	62	7.42		41	7.31		|	9	6.94		20	6.89	
103	|	62	7.42		39	7.34		|	9	6.94		27	6.90	
105	|	63	7.39		38	7:29		|	7	6.95		17	6.91	
107	|	63	7.39		36	7.30		|	7	6.95		19	6.92	
109	|	67	7.17		29	7.13		|	9	6.97		11	6.95	
111	|	67	7.17		42	7.14		|	9	6.97		6	6.87	
113	|	72	7.16		34	7.14		|	7	6.95		14	6.93	
115	↓	72	7.16		36	7.14		↓	7	6.95		7	6.88	

APPENDIX 1
(cont.)

Datum Number	Maternal (Hb) gm%	Maternal Artery			Maternal Vein			Fetal (Hb) gm%	Fetal Artery			Fetal Vein		
		P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg	P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg		P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg	P_{O_2} mm. Hg	pH	P_{CO_2} mm. Hg
123		72	7.16		42	7.17			7	6.95		9	6.89	
125	9.2	154	7.38		78	7.32		8.5	26	7.00		41	6.99	
127	↓	154	7.38		55	7.31		↓	26	7.00		41	6.98	
129	↓	130	7.34		52	7.32		↓	18	7.00		32	6.99	
131	↓	130	7.34		61	7.30		↓	18	7.00		35	6.98	
133	↓	116	7.36		64	7.34		↓	18	6.97		30	6.96	
135	↓	116	7.36		69	7.32		↓	18	6.97		23	6.95	
137	↓	119	7.38		50	7.31		↓	13	6.96		22	6.95	
139	↓	119	7.38		50	7.34		↓	13	6.96		22	6.95	
157	8.8	90	7.47	26	37	7.43	29	10.9	14	7.38	41	25	7.37	38
159	↓	90	7.47	26	39	7.43	25	↓	14	7.38	41	28	7.32	40
161	↓	75	7.44	28	35	7.40	35	↓	13	7.36	37	23	7.35	34
163	↓	75	7.44	28	34	7.40	31	↓	13	7.36	37	22	7.36	36
169	↓	90	7.47	26	37	7.43	29	↓	14	7.38	41	27	7.34	37
171	↓	90	7.47	26	37	7.43	29	↓	14	7.38	41	26	7.37	36
173	↓	90	7.47	26	39	7.43	25	↓	14	7.38	41	31	7.37	32
175	↓	90	7.47	26	39	7.43	25	↓	14	7.38	41	30	7.36	32
177	↓	75	7.44	28	35	7.40	35	↓	13	7.36	37	22	7.35	32
179	↓	75	7.44	28	35	7.40	35	↓	13	7.36	37	21	7.37	30
181	↓	75	7.44	28	34	7.40	31	↓	13	7.36	37	23	7.37	31
183	↓	75	7.44	28	34	7.40	31	↓	13	7.36	37	23	7.35	33
185	11.9	214	7.30	24	54	7.20	47	10.0	26	7.32	46	36	7.30	45
187	↓	214	7.30	24	49	7.20	44	↓	26	7.32	46	36	7.32	44
197	↓	285	7.34	28	56	7.27	37	↓	28	7.39	33	40	7.30	39
199	↓	285	7.34	28	58	7.26	31	↓	28	7.39	33	34	7.27	43
247	13.3	210	7.52	10	34	7.32	30	10.3	8	7.28	40	14	7.29	40
259	↓	214	7.55		40	7.38		↓	9	7.26		20	7.36	
283	10.2	120	7.27	32	44	7.25	38	9.1	16	7.38	40	26	7.38	36
285	↓	120	7.27	32	40	7.21	40	↓	16	7.38	40	24	7.36	38
295	↓	104	7.28	30	36	7.20	38	↓	10	7.30	44	38	7.32	38
297	↓	104	7.28	30	50	7.24	34	↓	10	7.30	44	37	7.32	36
303	↓	104	7.28		50	7.24		↓	10	7.29		38	7.33	
305	↓	104	7.28		50	7.24		↓	10	7.29		38	7.33	

procedure will not give accurate data because the oxygen dissociation curve used by Hellegers et al. to prepare their nomogram refers to freshly drawn goat blood and should not be applied to blood that is somewhat hemolysed and has been held in storage for 24 hours. For this reason the data are given as partial pressures and pH's. The conversion of these data to oxygen content is not recommended.

APPENDIX 2

Nitrous oxide (N_2O) and acetylene (C_2H_2) analyses of 84 acceptable sets of blood samples obtained from the perfusion of 23 placentas in 14 goats. The concentrations of N_2O and C_2H_2 are expressed as peak heights of the chromatographic record.

MA Maternal (carotid) artery.

MV Maternal (uterine) vein.

FA Fetal (umbilical) artery.

FV Fetal (umbilical) vein.

An estimate of the amount of N_2O and C_2H_2 can be obtained in the following way.

The amount of N_2O and C_2H_2 expressed as ml. / 100 ml. can be estimated by taking the observed peak height, and dividing it by the peak height given by a sample containing 1 volume % of N_2O or C_2H_2 ; i.e. 14 and 6.6 respectively.

Appendix 2

Datum Number	MA_{N_2O}	MV_{N_2O}	FA_{N_2O}	FV_{N_2O}	$MA_{C_2H_2}$	$MV_{C_2H_2}$	$FA_{C_2H_2}$	$FV_{C_2H_2}$
1	154	122	0	59	6	29	130	76
5	138	85	0	27	0	40	112	85
17	200	139	0	40	0	30	135	107
19	270	114	5	55	2	60	95	84
27	220	202	2	143	4	16	132	61
33	230	171	5	79	4	38	130	88
41	471	379	14	199	5	46	265	157
53	225	205	19	144	6	29	220	86
55	225	192	19	136	6	35	220	80
57	260	230	16	151	6	34	225	99
61	270	235	20	164	6	34	235	104
63	270	235	20	158	6	42	235	100
65	275	238	20	162	6	35	232	103
67	275	230	20	166	6	40	232	102
73	287	165	3	77	4	121	256	192
75	262	160	1	65	6	109	255	186
85	285	236	3	175	3	18	192	75
87	285	245	3	176	3	16	192	73
89	285	212	11	146	4	37	182	87
91	285	238	11	147	4	38	182	80
93	291	195	10	110	4	60	180	111
95	291	193	10	104	4	60	180	120
97	260	220	0	112	3	22	200	108
101	245	212	2	113	3	23	199	106
103	245	217	2	120	3	18	199	94
107	235	156	6	85	6	58	177	115

Appendix 2 (cont)

Datum Number	MA_{N_2O}	MV_{N_2O}	FA_{N_2O}	FV_{N_2O}	$MA_{C_2H_2}$	$MV_{C_2H_2}$	$FA_{C_2H_2}$	$FV_{C_2H_2}$
127	275	200	14	143	7	46	167	79
129	265	169	8	116	8	63	163	99
131	265	200	8	128	8	44	163	85
137	265	198	6	79	7	51	175	120
139	265	181	6	102	7	57	175	106
153	196	177	2	104	2	18	154	69
155	196	174	2	108	2	14	154	61
157	197	180	2	103	2	20	154	70
159	197	176	2	111	2	16	154	60
161	197	176	2	100	2	20	154	67
163	197	180	2	100	2	20	154	67
167	197	176	2	114	2	16	154	62
169	200	146	7	86	4	32	140	78
171	200	154	7	104	4	30	140	74
173	200	146	7	87	4	32	140	78
175	200	146	7	87	4	32	140	78
177	200	154	7	106	4	30	140	69
179	200	154	7	102	4	30	140	73
181	196	163	4	94	4	30	152	84
185	247	143	8	84	3	56	140	102
187	247	160	8	87	3	47	140	101
189	247	143	8	88	3	56	140	104
191	247	143	8	87	3	56	140	104
193	247	160	8	84	3	47	140	100
197	217	182	5	120	3	45	164	79
199	217	177	5	106	3	35	164	85

Appendix 2 (cont)

Datum Number	MA_{N_2O}	MV_{N_2O}	FA_{N_2O}	FV_{N_2O}	$MA_{C_2H_2}$	$MV_{C_2H_2}$	$FA_{C_2H_2}$	$FV_{C_2H_2}$
201	217	182	5	104	3	45	164	78
205	217	177	5	118	3	35	164	79
207	217	177	5	117	3	35	164	73
209	220	187	2	112	3	30	166	83
211	220	185	2	115	3	27	166	73
213	220	187	2	114	3	30	166	82
215	220	187	2	112	3	30	166	85
217	220	185	2	120	3	27	166	79
219	220	185	2	123	3	27	166	77
245	220	122	1	31	0	63	157	140
247	220	106	1		0	72	157	
249	220	122	1	32	0	63	157	120
251	220	122	1	33	0	63	157	136
253	220	106	1	32	0	72	157	128
255	220	106	1	33	0	72	157	136
269	230	135	1	30	1	58	152	152
271	230	132	1		1	61	152	142
273	230	135	1	27	1	58	152	132
277	230	132	1	27	1	61	152	132
283	223	138	4	89	5	69	194	128
285	223	139	4	72	5	76	194	129
287	223	138	4	87	5	69	194	120
289	223	138	4	88	5	69	194	122
291	223	139	4	70	5	76	194	123
293	223	139	4	75	5	76	194	133
303	230	180	1	138	3	26	194	82

Appendix 2 (cont)

Datum Number	MA_{N_2O}	MV_{N_2O}	FA_{N_2O}	FV_{N_2O}	$MA_{C_2H_2}$	$MV_{C_2H_2}$	$FA_{C_2H_2}$	$FV_{C_2H_2}$
305	230	180	1	134	3	26	194	84
307	222	146	4	111	7	56	183	109
309	222	146	4	113	7	56	183	102
311	222	146	4	112	7	56	183	106
317	226	146	4	90	2	68	194	127
329	226	184	4	128	2	25	194	82
343	226	187	4	134	2	24	194	83

APPENDIX 3

The $T^{M}T^{F}$ points for N_2O and C_2H_2 calculated from the data in appendix 2.

$$T^{M} = (MA - MV) / (MA - FA)$$

$$T^{F} = (FV - FA) / (MA - FA)$$

$$T^{\bar{M}} = 1/2 \, (T^{M}_{N_2O} + T^{M}_{C_2H_2})$$

$$T^{\bar{F}} = 1/2 \, (T^{F}_{N_2O} + T^{F}_{C_2H_2})$$

The ratio (R^{M}) of the umbilical ($\dot{Q}_F$) to uterine ($\dot{Q}_M$) blood flow is defined as

$$R^{M} = T^{M}/T^{F}$$

and

$$R^{\bar{M}} = \bar{T}^{M}/\bar{T}^{F}$$

APPENDIX 4

Hemodynamic data from the perfusion of 23 placentas in 14 goats showing how the flow ratios (R^{M}) were obtained.

The datum name represents the number of the experiment, the placenta and the particular sample, e.g., 11-R-2 means the 11th goat the right placenta and the second flow of that day. In some cases samples were taken from only one of the two umbilical veins draining a placenta. In these cases the datum name is followed by a subscripted 1, 2, 3 or 4. The umbilical flow ($\dot{Q}_F$) is the flow to 1 placenta only. The uterine flow ($\dot{Q}_M$) is the uterine flow associated with one placenta

Appendix 3

Datum Number	$T^{M}_{N_2O}$	$T^{M}_{C_2H_2}$	$T^{F}_{N_2O}$	$T^{F}_{C_2H_2}$	$R^{M}_{N_2O}$	$R^{M}_{C_2H_2}$	$T^{\bar{M}}$	$T^{\bar{F}}$	$R^{\bar{M}}$
1	0.208	0.186	0.383	0.436	0.542	0.426	0.197	0.410	0.480
5	0.384	0.357	0.196	0.241	1.96	1.48	0.37	0.216	1.722
17	0.305	0.222	0.200	0.207	1.535	1.071	0.268	0.204	1.314
19	0.589	0.624	0.189	0.124	3.120	5.043	0.608	0.157	3.873
27	0.083	0.094	0.647	0.555	0.128	0.169	0.0882	0.601	0.147
33	0.262	0.270	0.329	0.333	0.797	0.810	0.266	0.377	0.706
41	0.201	0.158	0.405	0.415	0.497	0.380	0.180	0.410	0.439
53	0.097	0.107	0.607	0.626	0.160	0.172	0.102	0.617	0.165
55	0.160	0.136	0.568	0.654	0.282	0.207	0.148	0.611	0.242
57	0.129	0.128	0.553	0.575	0.222	0.222	0.128	0.564	0.227
61	0.140	0.122	0.576	0.572	0.243	0.214	0.131	0.574	0.228
63	0.140	0.157	0.552	0.590	0.254	0.267	0.149	0.571	0.261
65	0.145	0.128	0.557	0.571	0.261	0.225	0.137	0.564	0.243
67	0.176	0.150	0.572	0.575	0.308	0.262	0.163	0.574	0.284
73	0.454	0.429	0.261	0.254	1.743	1.687	0.442	0.258	0.171
75	0.398	0.426	0.245	0.277	1.625	1.537	0.412	0.261	1.578
85	0.173	0.079	0.607	0.619	0.285	0.128	0.126	0.613	0.205
87	0.141	0.069	0.611	0.629	0.231	0.109	0.105	0.620	0.169
89	0.266	0.185	0.493	0.534	0.541	0.347	0.225	0.514	0.438
91	0.172	0.191	0.496	0.573	0.346	0.333	0.182	0.534	0.341
93	0.340	0.318	0.355	0.392	0.960	0.930	0.329	0.374	0.880
95	0.349	0.318	0.342	0.341	1.020	0.930	0.334	0.342	0.977
97	0.153	0.096	0.431	0.467	0.357	0.206	0.124	0.449	0.276
101	0.136	0.102	0.456	0.474	0.297	0.215	0.119	0.475	0.251
103	0.115	0.077	0.485	0.535	0.237	0.143	0.095	0.510	0.186
107	0.345	0.302	0.345	0.362	1.000	0.838	0.323	0.354	0.912

Appendix 3 (cont)

Datum Number	$T^{M}_{N_2O}$	$T^{M}_{C_2H_2}$	$T^{F}_{N_2O}$	$T^{F}_{C_2H_2}$	$R^{M}_{N_2O}$	$R^{M}_{C_2H_2}$	$T^{\bar{M}}$	$T^{\bar{F}}$	$R^{\bar{M}}$
127	0.287	0.244	0.494	0.550	0.581	0.443	0.265	0.522	0.508
129	0.373	0.355	0.420	0.413	0.880	0.859	0.364	0.416	0.875
131	0.253	0.232	0.466	0.503	0.542	0.461	0.242	0.484	0.500
137	0.259	0.262	0.282	0.327	0.917	0.800	0.260	0.304	0.855
139	0.324	0.298	0.371	0.411	0.875	0.724	0.311	0.391	0.795
153	0.0979	0.105	0.525	0.559	0.186	0.188	0.102	0.542	0.188
155	0.113	0.0789	0.546	0.612	0.208	0.129	0.096	0.579	0.166
157	0.0871	0.118	0.517	0.553	0.168	0.214	0.102	0.535	0.191
159	0.108	0.0921	0.558	0.618	0.193	0.149	0.100	0.588	0.170
161	0.0871	0.118	0.502	0.572	0.173	0.206	0.102	0.537	0.190
163	0.0871	0.118	0.523	0.539	0.167	0.219	0.102	0.531	0.192
167	0.108	0.0921	0.574	0.605	0.188	0.152	0.100	0.589	0.170
169	0.280	0.206	0.409	0.456	0.683	0.451	0.243	0.432	0.562
171	0.238	0.191	0.502	0.485	0.474	0.393	0.214	0.494	0.433
173	0.280	0.206	0.414	0.456	0.675	0.451	0.243	0.435	0.559
175	0.280	0.206	0.415	0.456	0.675	0.451	0.243	0.435	0.559
177	0.238	0.191	0.513	0.522	0.464	0.366	0.214	0.518	0.413
179	0.238	0.191	0.492	0.493	0.484	0.388	0.214	0.492	0.435
181	0.172	0.176	0.469	0.459	0.355	0.382	0.174	0.464	0.375
185	0.439	0.387	0.326	0.277	1.346	1.395	0.413	0.302	1.368
187	0.368	0.321	0.331	0.285	1.114	1.129	0.345	0.308	1.120
189	0.439	0.387	0.335	0.263	1.312	1.472	0.413	0.299	1.381
191	0.439	0.387	0.331	0.263	1.329	1.472	0.413	0.297	1.391
193	0.368	0.321	0.326	0.292	1.128	1.100	0.345	0.309	1.117
197	0.173	0.261	0.569	0.528	0.304	0.494	0.217	0.535	0.395
199	0.198	0.199	0.500	0.491	0.396	0.405	0.198	0.495	0.400

Appendix 3 (cont)

Datum Number	$T^{M}_{N_2O}$	$T^{M}_{C_2H_2}$	$T^{F}_{N_2O}$	$T^{F}_{C_2H_2}$	$R^{M}_{N_2O}$	$R^{M}_{C_2H_c}$	$T^{\bar{M}}$	$T^{\bar{F}}$	$R^{\bar{M}}$
201	0.173	0.261	0.490	0.534	0.354	0.488	0.217	0.512	0.424
205	0.198	0.199	0.559	0.528	0.354	0.376	0.217	0.544	0.399
207	0.198	0.199	0.554	0.565	0.357	0.352	0.198	0.560	0.354
209	0.151	0.166	0.504	0.509	0.300	0.325	0.159	0.506	0.314
211	0.161	0.147	0.518	0.571	0.310	0.258	0.154	0.544	0.283
213	0.151	0.166	0.514	0.515	0.295	0.321	0.159	0.514	0.309
215	0.151	0.166	0.504	0.497	0.300	0.333	0.154	0.500	0.308
217	0.161	0.147	0.541	0.534	0.297	0.276	0.159	0.538	0.296
219	0.161	0.147	0.555	0.546	0.289	0.270	0.154	0.500	0.280
245	0.448	0.401	0.137	0.108	3.267	3.706	0.424	0.122	3.475
247	0.521	0.459	0.137	0.108	3.800	4.235	0.490	0.122	4.016
249	0.448	0.401	0.142	0.185	3.155	2.168	0.424	0.163	2.540
251	0.448	0.401	0.146	0.134	3.068	2.993	0.424	0.140	3.029
253	0.521	0.459	0.142	0.185	3.669	2.481	0.490	0.163	3.006
255	0.521	0.459	0.142	0.185	3.669	3.481	0.490	0.140	3.500
269	0.415	0.378	0.127	0.066	3.276	5.700	0.397	0.097	4.092
271	0.428	0.397	0.127	0.066	3.379	6.000	0.412	0.097	4.247
273	0.415	0.378	0.114	0.132	3.640	2.864	0.397	0.123	3.228
277	0.428	0.397	0.114	0.132	3.754	3.008	0.412	0.123	3.350
283	0.388	0.339	0.388	0.349	1.000	0.970	0.364	0.378	0.963
285	0.384	0.376	0.311	0.344	1.235	1.092	0.380	0.327	1.162
287	0.388	0.339	0.379	0.392	1.020	0.864	0.364	0.385	0.945
289	0.388	0.339	0.384	0.381	1.010	0.890	0.364	0.383	0.950
291	0.384	0.376	0.301	0.376	1.270	1.000	0.380	0.339	1.121
293	0.384	0.376	0.324	0.323	1.180	1.160	0.380	0.324	1.173
303	0.218	0.210	0.598	0.586	0.365	0.205	0.169	0.592	1.173

Appendix 3 (cont)

Datum Number	$T^{M}_{N_2O}$	$T^{M}_{C_2H_2}$	$T^{F}_{N_2O}$	$T^{F}_{C_2H_2}$	$R^{M}_{N_2O}$	$R^{M}_{C_2H_2}$	$T^{\bar{M}}$	$T^{\bar{F}}$	$R^{\bar{M}}$
305	0.218	0.100	0.581	0.576	0.375	0.174	0.169	0.578	0.292
307	0.349	0.279	0.491	0.420	0.710	0.662	0.314	0.455	0.690
309	0.349	0.279	0.500	0.460	0.698	0.607	0.314	0.480	0.654
311	0.349	0.279	0.496	0.438	0.704	0.637	0.314	0.467	0.672
317	0.384	0.337	0.393	0.353	0.980	0.955	0.360	0.373	0.965
329	0.188	0.111	0.562	0.589	0.335	0.188	0.149	0.575	0.259
343	0.174	0.105	0.580	0.584	0.300	0.180	0.139	0.582	0.239

Appendix 4

Datum Number	Datum Name	$\dot{Q}_F$/placenta ml./min.	$\dot{Q}_M$/placenta ml./min.	FAP mm. Hg	MAP mm. Hg	Pressure drop across occlusion mm. Hg
1	1-1	290	604	78		0
5	1-2	210	122	98		0
17	2-3	140	106	95		0
19	3-1	390	101	78		0
27	4-R-1	130	884	43		0
33	4-L-2	231	327	82		0
41	6-2	355	808	35	90	0
53	8-L-3	260	1575	40	70	0
55	8-R-3	200	826	40	70	0
57	8-L-4	260	1145	40	70	0
61	8-L-5	260	1140	45	70	0
63	8-R-5	200	766	45	70	0
65	8-L-6	260	1070	42	70	0
67	8-R-6	200	704	42	70	0
73	9-3	376	2199	40	50	20
75	9-5	376	238	40	60	0
85	11-R-1	102	497	27	110	0
87	11-L-1	85	503	27	110	0
89	11-R-2	184	420	47	90	20
91	11-L-2	180	528	47	90	20
93	11-R-3	265	301	52	55	60
95	11-L-3	240	245	52	55	60
97	12-R-1	75	271	35	75	35
101	12-R-2	75	299	35	75	30
103	12-L-2	75	403	35	75	30
107	12-L-3	250	274	67	80	10

Appendix 4 (cont)

Datum Number	Datum Name	$\dot{Q}_F$/placenta ml. /min.	$\dot{Q}_M$/placenta ml. /min	FAP mm. Hg	MAP mm. Hg	Pressure drop across occlusion mm. Hg
127	14-L-1	215	423	40	80	0
129	14-R-2	257	293	58	80	0
131	14-L-2	257	514	58	80	0
137	14-R-4	303	354	75	80	0
139	14-L-4	303	381	75	80	0
153	17-R-4	100	532	50	85	0
155	17-L-4	100	602	50	85	0
157	17-R-1	97	508	50	85	0
159	17-L-1	116	682	50	85	0
161	17-R-1	37	508	50	85	0
163	17-R-1_2	59	508	50	85	0
167	17-L-1_4	90	682	50	85	0
169	17-R-2	185	329	68	75	0
171	17-L-2	213	492	68	75	0
173	17-R-2_1	77	321	70	75	0
175	17-R-2_2	108	321	60	75	0
177	17-L-2_3	60	497	70	75	0
179	17-L-2_4	153	497	60	75	0
181	17-R-3	150	400	65	75	0
185	18-R-1	204	149	50	40	60
187	18-L-1	195	174	50	40	60
189	18-R-1_1	111	147	50	40	60
191	18-R-1_2	93	147	50	40	60
193	18-L-1_3	56	174	55	40	60
197	18-R-2	128	324	67	70	10
199	18-L-2	170	425	67	70	10

Appendix 4 (cont)

Datum Number	Datum Name	$\dot{Q}_F$/placenta ml./min.	$\dot{Q}_M$/placenta ml./min.	FAP mm. Hg	MAP mm. Hg	Pressure drop across occlusion mm. Hg
201	$18\text{-R-}2_1$	85	324	66	70	10
205	$18\text{-L-}2_3$	50	464	71	70	10
207	$18\text{-L-}2_4$	120	464	65	70	10
209	18-R-3	101	322	63	70	0
211	18-L-3	100	353	63	70	0
213	$18\text{-R-}3_1$	59	327	63	70	0
215	$18\text{-R-}3_2$	42	327	63	70	0
217	$18\text{-L-}3_3$	32	329	63	70	0
219	$18\text{-L-}3_4$	68	329	63	70	0
245	19-R-1	175	50	50	30	50
247	19-L-1	175	44	50	30	50
249	$19\text{-R-}1_{f1}$	88	63	50	30	50
251	$19\text{-R-}1_{f2}$	88	63	50	30	50
253	$19\text{-L-}1_1$	88	54	50	30	50
255	$19\text{-L-}1_2$	88	54	50	30	50
269	19-R-3	150	37	80	45	25
271	19-L-3	150	35	80	45	25
273	$19\text{-R-}3_1$	75	37	80	45	25
277	$19\text{-L-}3_1$	75	35	80	45	25
283	20-R-1	250	260	55	50	30
285	20-L-1	270	232	55	50	30
287	$20\text{-R-}1_1$	150	264	55	50	30
289	$20\text{-R-}1_2$	100	264	55	50	30
291	$20\text{-L-}1_3$	120	235	55	50	30
293	$20\text{-L-}1_4$	150	235	55	50	30
303	$20\text{-L-}2_3$	48	278	35	60	0

Appendix 4 (cont)

Datum Number	Datum Name	$\dot{Q}_F$/placenta ml. /min.	$\dot{Q}_M$/placenta ml. /min.	FAP mm. Hg	MAP mm. Hg	Pressure drop across occlusion mm. Hg
305	$20\text{-L-}2_4$	32	278	35	60	0
307	$20\text{-L-}3$	181	263	57	70	0
309	$20\text{-L-}3_3$	124	275	57	70	0
311	$20\text{-L-}3_4$	57	275	57	70	0
317	$20\text{-R-}0_B$	250	259	55	50	30
329	$20\text{-R-}30_B$	80	305	35	60	0
343	$20\text{-L-}30_B$	80	332	35	60	0

only. The mean umbilical arterial pressure (FAP) has been corrected for the pressure drop between the point of measurement and the umbilical arteries themselves. The mean uterine arterial pressure (MAP) is measured at a femoral artery. The pressure drop across the maternal abdominal aortic occlusion is the difference between mean carotid and mean femoral arterial pressure.

APPENDIX 5

The wet weights of the 20 adult goats, and their contained fetuses, placentas, and uteri, used to obtain the data presented in appendices 1-4. Where twins occur the right fetus and placenta is reported first. The number of cotyledons on each placenta is also reported.

APPENDIX 6

The calculation of the $T^{M}_{T}{}^{F}$ line of a concurrent and countercurrent exchanger with shunts of 36% and 23% and the flow distribution specified by Power et al. (71) by the method of Faber (27). According to Power et al. (71) the maternal to fetal flow ratios in each of 5 equal portions of the near term sheep placenta are, 0.242, 0.456, 0.726, 1.318 and 2.165. The 5 sections and the distribution of flow within each section can be represented in the following way:

$\dot{Q}_F/\dot{Q}_M = R^M$	A	B	C	D	E
	1.00	1.00	1.00	1.00	1.00
	0.24	0.46	0.73	1.32	2.26

Appendix 5

Goat	Wt. of Mother Kg	Fetal age days	Fetal wt. gms.	Placental wt. gms.	Number of coty-ledons	Uterine wt. gms.	Wt. of conceptus gms.
1	54.5	124					4734
2	64.9	126	2381	907		1134	4422
3	49.9	132	2041	1134		539	3714
4	46.7	104	765 737	567 680		992	3741
5	51.7		1446	1021		964	3431
6	62.6		2098	907		2126	5131
7	46.3						
8	66.2	137	3430 2722	454 454		1814	8874
9	45.4	147	2070	624	150	1616	4310
10	62.6		595	2098	104	907	3600
11	59.0	121	2041 1729	567 454	84 87	1219	6009
12	61.2	121	1616 1786	765 851	53 74	1162	6180
13	36.6		2665 2665	624 765	95 92	1134	7853
14	49.4	126	1503 1474	425 312	60 64	1021	4734
15	45.4		1644 1446	680 765	69 69	879	5413
16	31.8		3686	936	85	595	5217
17	59.0	123	1503 1843	510 624	72 78	1077	5558
18	63.5	128	1729 1531	737 567	80 71	1134	5698
19	35.4	117	1162	510	114	340	2012
20	40.8	120	1361 1389	595 567	68 66	907	4825

It will be noticed that the fetal flow is evenly distributed throughout the 5 sections. This arbitrary assumption is necessitated by the fact that Power et al. give no information as to the extent whereby each flow is responsible for the uneven distribution. In this circumstance the simplest assumption is that one flow is responsible. The numerators and denominators of each ratio can be normalized to sum to 1 without changing the ratio of the flow distributions between A, B, C, D and E.

	A	B	C	D	E
R^M	0.20	0.20	0.20	0.20	0.20
	0.05	0.09	0.15	0.27	0.44

Five ratios of total fetal to maternal flow (R^M) will be considered. These are zero, 0.5, 1.0, 2.0 and infinity. It is necessary to calculate the maternal venous concentration (C_{MV}) of an infinity diffusible substance passing from the maternal to the fetal side for each of the 5 sections assuming first a countercurrent then a concurrent arrangement of exchanging vessels. In all cases C_{FA} will be assumed to be zero and C_{MA} will be assumed to be 1. For the countercurrent model where R^M is less than or equal to unity $C_{MV} = (1-R^M)$ and where R^M is greater than unity, $C_{MV}=0$. When the vessels are arranged in a concurrent configuration $C_{MV} = 1/(1 + R^M)$.

Case 1. $R^M = 0.5$ and $\dot{Q}_F = 1$, $\dot{Q}_M = 2$.

Dividing the flows among the 5 sections and calculating the maternal venous concentrations for each section we have:

		A	B	C	D	E
	$\dot{Q}_M$	0.10	0.18	0.30	0.57	0.88
	$\dot{Q}_F$	0.20	0.20	0.20	0.20	0.20
	R^M	2.00	1.11	0.67	0.35	0.23
Countercurrent	C_{MV}	0.00	0.00	0.33	0.65	0.77
Concurrent	C_{MV}	0.33	0.47	0.60	0.74	0.81

The concentration in the mixed venous blood from all sections C^*_{MV} is found by multiplying the $\dot{Q}_M$ by the C_{MV} for each section and dividing the sum of these quantities by the total maternal flow to the placenta. For case 1,

Countercurrent $C^*_{MV} = 0.574$

Concurrent $C^*_{MV} = 0.716$

Case 2. $R^M = 1.0$ and $\dot{Q}_M = \dot{Q}_F = 1.0$

		A	B	C	D	E
	$\dot{Q}_M$	0.05	0.09	0.15	0.27	0.44
	$\dot{Q}_F$	0.20	0.20	0.20	0.20	0.20
	R^M	4.00	2.22	1.34	0.70	0.46
Countercurrent	C_{MV}	0.00	0.00	0.00	0.30	0.54
Concurrent	C_{MV}	0.20	0.31	0.43	0.59	0.68

It follows that:

Countercurrent $C^*_{MV} = 0 \cdot 319$

Concurrent $C^*_{MV} = 0 \cdot 561$

Case 3. $R^M = 2$ and $\dot{Q}_F = 2$, $\dot{Q}_M = 1$.

		A	B	C	D	E
	$\dot{Q}_M$	0.05	0.09	0.15	0.27	0.44
	$\dot{Q}_F$	0.40	0.40	0.40	0.40	0.40
	R^M	4.00	2.22	1.34	0.70	0.46
Countercurrent	C_{MV}	0.00	0.00	0.00	0.30	0.54
Concurrent	C_{MV}	0.20	0.31	0.43	0.59	0.68

It follows that:

Countercurrent $C^*_{MV} = 0 \cdot 40$

Concurrent $C^*_{MV} = 0 \cdot 399$

The $T^M T^F$ coordinates for cases 1, 2 and 3 for a countercurrent and a concurrent model can be found in the following way:

$$T^M = 1 - C^*_{MV} \text{ and } T^F = T^M / R^M$$

The following table can be constructed.

	$R^M = 0 \cdot 5$		$R^M = 1 \cdot 0$		$R^M = 2 \cdot 0$	
	con-current	counter-current	con-current	counter-current	con-current	counter-current
C^*_{MV}	0.716	0.574	0.561	0.319	0.399	0.040
C_{MA}	0.284	0.426	0.439	0.681	0.601	0.960
T^M	0.284	0.426	0.439	0.681	0.601	0.960
T^F	0.590	0.880	0.442	0.690	0.296	0.482
T^M_c	0.182	0.273	0.281	0.436	0.385	0.614
T^F_c	0.454	0.678	0.340	0.531	0.228	0.371

Where T_c^M and T_c^F are the $T^M T^F$ values corrected for a maternal shunt of 36% and a fetal shunt of 23% so that:

$$T_c^M = T^M(1-0\cdot 36) = 0\cdot 64\, T^M$$

$$T_c^F = T^F(1-0\cdot 23) = 0\cdot 77 T^F$$

For the countercurrent and concurrent models the $T^M T^F$ coordinates at R^M values of zero and infinity are as follows:

When R^M = zero, $T_c^M = 0\cdot 0$ and $T_c^F = 0\cdot 77$

When R^M = infinity, $T_c^M = 0\cdot 64$ and $T_c^F = 0\cdot 0$

The $T^M T^F$ diagram for these values of $T_c^M T_c^F$ is shown in Figure 15.

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