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## FETAL HOMEOSTASIS IN RELATION TO PLACENTAL WATER EXCHANGE

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### Résumé

L'HOMEOSTASIE FŒTALE, EN RELATION AVEC LES ECHANGES D'EAU TRANSPACENTAIRES. — La croissance du fœtus nécessite un flux transplacentaire continu d'eau et de substances dissoutes. On sait que plusieurs de ces substances sont transportées à travers le placenta par des mécanismes actifs. Mais on doit supposer que les matières inertes sont transportées par un mécanisme de filtration et de diffusion et que le flux d'eau est un processus osmotique.

Chez le mouton, le plasma maternel est hyperosmotique par rapport au plasma fœtal (Meschia *et al.*, 1957 ; Armentrout *et al.*, 1977). Néanmoins, le flux d'eau va du sang maternel au sang fœtal. Pour expliquer ce paradoxe osmotique, nous avons analysé les paramètres de la membrane placentaire du mouton.

Nous avons utilisé des fœtus d'agneaux portant des cathéters implantés chroniquement. Le coefficient de filtration osmotique, les perméabilités diffusionnelles des matières inertes (principalement  $\text{Na}^+$  et  $\text{Cl}^-$ ) et les concentrations des solutés ayant un rôle osmotique furent mesurés. Les coefficients de réflexion osmotique (Staverman, 1951) des corps dissous transportés activement furent évalués à partir des données de Boyd *et al.* (1976) selon la méthode de Renkin (1954). Les équations de Kedem et Katchalsky (1958, 1961) furent adoptées et nous avons substitué les flux de l'eau et des solutés inertes ( $\text{NaCl}$ ) calculés pour l'agneau fœtal pendant la gestation normale. Ainsi on a pu résoudre les équations permettant d'obtenir le coefficient de filtration ( $L_p S = 4.7 \cdot 10^{-8} \text{ cm}^5 \text{ dyne}^{-1} \text{ sec}^{-1} \text{ kg fœtus}^{-1}$ ) et le coefficient de réflexion osmotique de  $\text{NaCl}$  ( $\delta_{\text{NaCl}} = 0.7$ ).

Nous en avons conclu que la pression osmotique des électrolytes ( $\text{NaCl}$ ) qui sont présents dans le plasma maternel en concentration plus élevée que dans le plasma fœtal est compensée par la pression osmotique des corps transportés activement dont la différence de concentration est de sens opposé et plus petite et dont le coefficient de réflexion est plus grand. Il y existe aussi une faible pression hydrostatique de 20 mm Hg environ (Conrad et Faber, 1977).

Ces résultats étant obtenus par la substitution des flux normaux d'eau et d'électrolytes dans les équations de filtration et de diffusion il fallait les confirmer par d'autres expériences. Nous avons augmenté les flux d'eau et d'électrolytes (huit fois et trois fois) en évacuant

au-dehors l'urine du fœtus au moyen d'un cathéter permanent implanté dans la vessie du fœtus. Onze expériences de drainage prolongé donnèrent des valeurs du coefficient de réflexion d'électrolyte (moyenne  $0.83 \pm 0.18$ , S.D.) en bon accord avec celles obtenues auparavant.

Il résulte de la théorie que la perméabilité diffusionnelle et le coefficient de réflexion osmotique des électrolytes sont les limitations principales de l'accroissement du fœtus du mouton, et non le coefficient de filtration. Les expériences avec les isotopes  $^{22}\text{Na}^+$  et  $^{36}\text{Cl}^-$  ont démontré que les perméabilités diffusionnelles des électrolytes augmentent en proportion de l'accroissement fœtal, en accord avec la théorie.

Le fœtus du mouton peut modifier les flux d'eau et d'électrolytes par l'action de la vasopressine sur la membrane placentaire. La perfusion intraveineuse de longue durée de 8-11 unités par jour par kg de fœtus entraîna une diminution du coefficient de réflexion d'électrolytes de 0.8 à 0.6 ( $P < 0.03$ ). Dans toutes les expériences de drainage combinées il existait une forte corrélation négative entre l'osmolarité de l'urine fœtale et le coefficient de réflexion calculé pour la même expérience.

*« On y verra de ces sortes de demonstrations, qui ne produisent pas une certitude aussi grande que celles de Geometrie, et qui mesme en different beaucoup, puisque au lieu que les Géometres prouvent leurs Propositions par des Principes certains et incontestables, icy les Principes se verifient par les conclusions qu'on en tire ; la nature de ces choses ne souffrant pas que cela se fasse autrement. »*

Christian HUYGENS (1690)

## Introduction

It is the purpose of this paper to determine the permeability constants for the placenta of the sheep as defined by the formalism of Kedem and Katchalsky (1958, 1961).

The strategy employed is the following. It is assumed that water and inert solutes (such as electrolytes) flow across the barrier under the influence of hydrostatic and osmotic forces only. It is further assumed that the placental membrane, on occasion aided by the metabolism of the fetus, maintains a concentration difference of actively transported solutes and their derivatives across the barrier. We will try to demonstrate that it is only possible to account for the normal influxes of water and inert electrolytes during gestation if one assigns specific values to the permeability constants of the placental membranes. The validity of the analysis is confirmed by new data that show that when the transplacental fluxes are experimentally increased, above their normal values, the same membrane parameters continue to apply. Finally, we present evidence that the sheep fetus has some control over its water

and electrolyte acquisition by a mechanism that affects the membrane parameters.

### Assumptions about water

It is assumed that the water flow  $q_w$  across the placenta consists of flows that are contributed by three pressures and may be represented by

$$q_w = L_p S (\Delta p - \sum_i \sigma_i RT \Delta C_i - \sum_a \sigma_a RT \Delta C_a) \quad (1)$$

ml·sec<sup>-1</sup>·kg<sup>-1</sup>.

The factor  $L_p S$  is the filtration coefficient of the placental membrane,  $L_p$  the water flow per cm<sup>2</sup> of membrane per dyne/cm<sup>2</sup> pressure difference and  $S$  the surface area of the placental membrane of a sheep fetus of 1 kg weight. (The placental surface area is assumed proportional to the weight of the fetus in the last trimester of gestation.)

The first term is the contribution made by a hydrostatic pressure difference, if any, between maternal and fetal plasma. If there is a difference also in the colloid osmotic pressures of the plasma, then that difference

is included in  $\Delta p$ , (Kedem and Katchalsky, 1961).

The contributions made by the osmotic pressures exerted by crystalloid solutes are represented by the second and third terms. The osmotic pressures exerted by such non-colloid solutes may be less than the value of  $RT\Delta C$  that is predicted by the law of van't Hoff (where  $R$  and  $T$  are the gas constant and the absolute temperature and where  $\Delta C$  is the concentration difference across the placental barrier; we use the concentration *difference*,  $\Delta C$ , since we are only interested in the *difference* in osmotic pressures between maternal and fetal plasma). Staverman's reflection coefficient  $\sigma$  is defined as that fraction of the theoretic osmotic pressure that is actually exerted by a given solute across a membrane that is not entirely impermeable to that solute (Staverman, 1951).

#### Assumptions about solutes.

All solutes are separated into two broad classes in equation 1. Certain solutes, subscripted *a*, are transferred into the fetus by active transport or are derived from actively transferred precursors, or make use of carrier mechanisms. Their transfer does

not depend on filtration or diffusion. All known solutes in this class are identified by the subscript *a* and listed in Table 1. Evidence for active transport across the barrier is fetal accumulation against a concentration gradient. There are a few solutes however, subscripted *i* to denote "inert", for which there is no evidence of specialized transport. They are presumably transferred into the fetus by diffusion and/or ultrafiltration. This class consists of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ , and  $\text{Mg}^{++}$ ; the  $\text{Na}^+$  and  $\text{Cl}^-$  concentrations constitute 98% of the total plasma concentration of inert solutes. Often, therefore, the sum of the sodium and chloride concentrations is used instead of the total inert solute concentration. The sum of the influxes ( $\Sigma q_i$ ) of inert solutes is governed by the equation:

$$\Sigma q_i = \Sigma (PS_i \Delta C_i + [1 - \sigma_i] C_i q_w) \quad (2)$$

mM·sec<sup>-1</sup>·kg<sup>-1</sup>

where  $P$  is the diffusional permeability of the solute *i* (cm/sec.),  $C_i$  the average concentration of the solute *i* in fetal and maternal plasmas, and where the other symbols have the same meaning as in equation 1. The first term in equation 2 is the contribution

Table 1. The osmotic pressures exerted by solutes that are actively transported or that for other reason do not depend on diffusion or ultrafiltration for their transfer into the fetus.

| Solute               | Concentration mM/kg water |       |                              | $\sigma_a$ | $\Delta \pi_a$ (1)<br>mm Hg    |
|----------------------|---------------------------|-------|------------------------------|------------|--------------------------------|
|                      | Maternal                  | Fetal | $= \Delta C_a$               |            |                                |
| Lactate (2)          | 4.95                      | 3.54  | + 1.41                       | 0.95       | + 26.0                         |
| Fructose (3)         | 0.00                      | 1.75  | - 1.75                       | 0.998      | - 33.9                         |
| Amino acids (4)      | 3.40                      | 6.30  | - 2.90                       | 0.85 (5)   | - 46.8                         |
| HCO <sub>3</sub> (6) | —                         | —     | - 2.11                       | 0.89       | - 36.4                         |
| Urea (6)             | 6.54                      | 7.28  | - 0.74                       | 0.78       | - 11.2                         |
| Ca <sup>++</sup> (6) | 2.26                      | 3.01  | - 0.75                       | 0.98       | - 14.3                         |
| Phosphate (6)        | 0.52                      | 0.76  | - 0.24                       | 1.00       | - 4.7                          |
| Glucose (6)          | 3.28                      | 1.28  | + 2.00                       | 0.998      | + 38.7                         |
| Total difference:    |                           |       | $\Sigma \Delta C_a = - 5.08$ |            | $\Delta \Sigma \pi_a = - 82.6$ |

(1) Calculated from  $\sigma_a RT \Delta C_a / 1337$ .

(2) From Kaiser and Cummings, 1958, water content correction added.

(3) From Tsoulos *et al.*, 1971, water content correction added.

(4) From Lemons, 1976 and Jones, 1977.

(5) Estimated mean reflection coefficient for all amino acids.

(6) From Armentrout *et al.*, 1977. Plasma water content corrections were estimated from plasma protein data of the same source., 6.65 and 3.42 g/100 ml plasma in maternal and fetal blood respectively.

of the diffusional inflow under the influence of the concentration difference  $\Delta C_i$  across the placental barrier and the second term is the contribution to the flow of inert solutes across the membrane by ultrafiltration. The concentration of the solute in the ultrafiltrate is not equal to  $C_i$ , but is less by the factor  $(1-\sigma_i)$ .

*Assumptions about the membrane*

In the derivations (Kedem and Katchalsky, 1958, 1961) that lead to equations such as #1 and #2 assumptions are made with regard to the nature of the membrane of which the most important ones are that the membrane is homogeneous, that exchange is isothermal, and that there is no net electric current flowing through the membrane. An electrical potential difference and charge selectivity of the membrane are permitted, however. If salts (such as NaCl) rather than the individual ions ( $Na^+$  and  $Cl^-$ ) are considered, the definitions of the permeability coefficients retain their validity (Kedem and Katchalsky, 1961). No net current flows across the placenta, since fetal capacitance is infinitesimal, and exchange can be shown to be isothermal to within a fraction of a millidegree Centigrade (Conrad and Faber, 1977). Whether the placental membrane of the sheep is (sufficiently) homogeneous however, is, of course, uncertain.

*The data*

It is plain from the number of symbols in equations 1 and 2 that a vast amount of information is needed before only two unknowns are left, the maximum number of unknowns that can be solved from 2 equations. The necessary information is available, however, and will be accumulated in Table 2 as it is presented.

a) The filtration coefficient,  $L_p S$ .

The filtration coefficient is of primary concern in any theory of transplacental water and electrolyte flow. The necessary experiments were performed in our laboratory, on sheep fetuses with indwelling catheters (Armentrout *et al.*, 1977). Maternal or fetal plasmas were made hypertonic by the i.v. infusion of strongly hypertonic mannitol or sucrose solutions. Calculated transplacental water flow  $q_c$  was the product of placental

Table 2. Experimental values used in equations 1, 2 and 3. Sheep, last trimester of gestation. Differences are given as maternal minus fetal. Flux and permeability per kg fetal weight, concentration per kg plasma water.

| Quantity   | Value  | Source  |
|--|--|---|
| Osmotic conductivity ( $\sigma L_p S$ )                            | $3.92 \cdot 10^{-8} \text{ cm}^2 \text{ sec}^{-1} \text{ dyne}^{-1} \text{ kg}^{-1}$ | Armentrout <i>et al.</i> , 1977.                |
| Diffusion permeability ( $PS_{NA+}$ )<br>( $PS_{CL-}$ )            | $5.53 \cdot 10^{-3} \text{ ml} \cdot \text{sec}^{-1} \text{ kg}^{-1}$                | Unpublished experiments in authors' laboratory. |
|  | $1.04 \cdot 10^{-2} \text{ ml} \cdot \text{sec}^{-1} \text{ kg}^{-1}$                |   |
| Normal gestational water influx ( $q_w$ )                          | $2.85 \cdot 10^{-4} \text{ ml} \cdot \text{sec}^{-1} \text{ kg}^{-1}$                | Conrad and Faber, 1977.                         |
| Normal gestational salt influx ( $\Sigma q_i$ )                    | $84.2 \text{ nM} \cdot \text{sec}^{-1} \text{ kg}^{-1}$                              | Conrad and Faber, 1977.                         |
| Difference in inert solute plasma conc. ( $\Sigma \Delta C_i$ )    | $13.1 \text{ mM/kg water}$   | Unpublished experiments in authors' laboratory. |
| Average plasma concentration of inert solutes ( $C_i$ )            | $264 \text{ mM/kg water}$  |   |
| Difference in "active" solute plasma conc. ( $\Sigma \Delta C_a$ ) | $-5.1 \text{ mM/kg water}$   | Table 1.  |
| Reflection coefficient of "active" solutes ( $\sigma_a$ )          | 0.85   | Table 1.  |
| Difference in plasma osmolality ( $\Delta Osm$ )                   | $2.4 \text{ mOsm/kg water}$  | Unpublished experiments in authors' laboratory. |

blood flow and the arteriovenous difference in blood water content. The latter quantity was estimated from the arteriovenous differences in the concentration of marker solutes for which  $\text{Na}^+$ ,  $\text{Cl}^-$  and  $\text{K}^+$  were used. The slope of the regression of transplacental water flow as a function of the transplacental difference in osmosity is a measure of the filtration coefficient, but an impure one because the marker solutes are not wholly impermeable. It can be shown that the slope of the regression,  $dq_c/d(\text{RT}\Delta C)$ , is not  $L_p S$ , but is to a good approximation equal to  $\sigma_i L_p S$ , where  $\sigma_i$  is again the reflection coefficient of the inert marker solute,  $\text{Na}^+$ , or  $\text{Cl}^-$ , or  $\text{K}^+$  (Conrad and Faber, 1977). We therefore have a third equation:

$$dq_c/d(\text{RT}\Delta C) = \sigma_i L_p S, \text{ cm}^5 \cdot \text{sec}^{-1} \cdot \text{dyne}^{-1} \cdot \text{kg}^{-1} \quad (3)$$

where the calculated water flow ( $q_c$ ) per unit osmotic gradient across the barrier ( $\text{RT}\Delta C$ ) is known from the osmotic experiments (Armentrout *et al.*, 1977). Its value is entered in Table 2.

b) The diffusion permeability of inert solutes,  $\text{PS}_i$ .

The diffusion permeability in the sheep placenta was measured also by Armentrout *et al.* (1977) by a straight-forward application of isotope techniques. Since  $\text{Na}^+$  and  $\text{Cl}^-$  constitute 98% of the total concentrations of inert electrolytes in fetal and maternal sheep plasmas, only the permeabilities of these two ions were determined. The basis for the calculation was equation 2, since when the concentration difference  $\Delta C_i$  is very large, as is the case in isotope studies, the contribution of ultrafiltration, the second term on the RHS in equation 2, becomes negligibly small. The amount of isotope traversing the barrier in the course of the measurement was estimated from the decrease in fetal plasma concentration and an assumed distribution volume of  $\text{Na}^+$  and  $\text{Cl}^-$ . Quite recently, we determined the fetal distribution volumes of these ions and found them to be very much larger than those previously assumed. As a consequence, the permeabilities of  $\text{Na}^+$  and  $\text{Cl}^-$  had to be revised; the revised values are listed in Table 2.

c) The water flux  $q_w$  and the salt flux  $q_s$ .  
The magnitude of the transplacental fluxes is very well established by analyses of fetal compositions (Field and Suttle, 1967) and

fetal weights (Barcroft, 1947) during the normal course of gestation in the sheep. The calculations of water flux, corrected for metabolically acquired water, and electrolyte flux ( $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{K}^+$ , and  $\text{Mg}^{++}$ ) have been described in detail elsewhere (Conrad and Faber, 1977). The results are listed in Table 2.

d) The concentration differences  $\Delta C_i$  and the average concentration  $C_i$  of the inert solutes ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{++}$  and  $\text{Cl}^-$ ).

The concentrations of inert electrolytes in fetal and maternal plasma have been determined by direct chemical measurement. The data, listed in Table 2, are, like all reported concentrations, expressed per kg plasma water; the laboratory results were corrected for plasma protein space to obtain these values.

e) The osmotic pressure exerted by the "active" solutes.

The concentrations of the "active" solutes were determined by direct chemical measurement in samples from fetuses and ewes indwelling catheters. Literature data from fetuses that were acutely studied, but were in good condition have also been used (Table 1). The reflection coefficients  $\sigma_a$  were calculated by application of the Renkin equation (Renkin, 1954) to the molecular radii of the solutes as calculated according to Durbin (1960) with a water radius of  $1.65 \cdot 10^{-8}$  cm (Bean, 1972) and an equivalent pore radius of the sheep placenta estimated at  $4.55 \cdot 10^{-8}$  cm on the basis of data collected and interpreted by Boyd *et al.* (1976), see Conrad and Faber (1977). The concentration-weighted average reflection coefficient  $\sigma_a$  was 0.845 (Table 1).

The total difference in "active" solute concentration between maternal and fetal plasma during normal gestation was calculated to be  $-5.08$  mM/kg water (Table 1).

#### Computations based on normal gestational transfer of water and salt in sheep

The data in Table 2 can be used with equations 1, 2, and 3 to calculate the values of the permeability parameters  $L_p S$ ,  $\text{PS}_i$ , and  $\sigma_i$ . In the computation  $\text{Na}^+$  and  $\text{Cl}^-$  are treated as the salt  $\text{NaCl}$  with a diffusional permeability of  $7.96 \cdot 10^{-3}$  ml $\cdot$ sec $^{-1}$  $\cdot$ kg $^{-1}$  (the average permeability of  $\text{Na}^+$  and  $\text{Cl}^-$ ) and

the reflection coefficient of NaCl is assumed to be the inert solute reflection coefficient  $\sigma_i$ , i.e. the contributions of  $K^+$  and  $Mg^{++}$  to  $\sigma_i$  are ignored.

The results of the computation are graphically shown in Figure 1. The equations were solved for a variety of transplacental water fluxes ( $q_w$ ) and osmolality gradients, ( $\Delta Osm$ ). Since the normal transplacental water flow is  $1.71 \cdot 10^{-2} \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ , and the normal transplacental osmolality gradient (M-F) is  $2.39 \text{ mOsm/kg}$  water, the inert solute reflection coefficient must be of the order of 0.7 and the normal hydrostatic pressure difference between maternal and fetal placental plasma must be of the order of 20 mm Hg. The fact that these values differ from those reported previously (Conrad and Faber, 1977) is almost entirely due to the revised sodium and chloride diffusion permeabilities. Since  $\sigma_i = 0.7$ , and  $L_p S RT\sigma_i = 61$ ,  $L_p S$  is  $5.6 \cdot 10^{-8} \text{ cm}^5\cdot\text{sec}^{-1}\cdot\text{dyne}^{-1}\cdot\text{kg}^{-1}$ .

**Constraints on fetal growth**

Given the values of the placental permeability parameters, fetal growth is of course fixed at the value (Barcroft, 1947) on the basis of which fetal water and electrolyte acquisitions were estimated. It was assumed that fetal growth, expressed as grams gained per day per kg fetal weight, was constant, since that appeared to be approximately true in the last third of gestation. That must mean then that the permeabilities ( $L_p S$  and  $PS_i$ ) also remain constant if expressed per kg weight. Thus, the results predicted that placental permeability should be approximately proportional to fetal weight and this prediction was confirmed for the diffusional permeabilities of  $Na^+$  and  $Cl^+$  (Armentrout *et al.*, 1977).

Once the permeability parameters were known, it became possible to investigate which of them most constrains the rate at

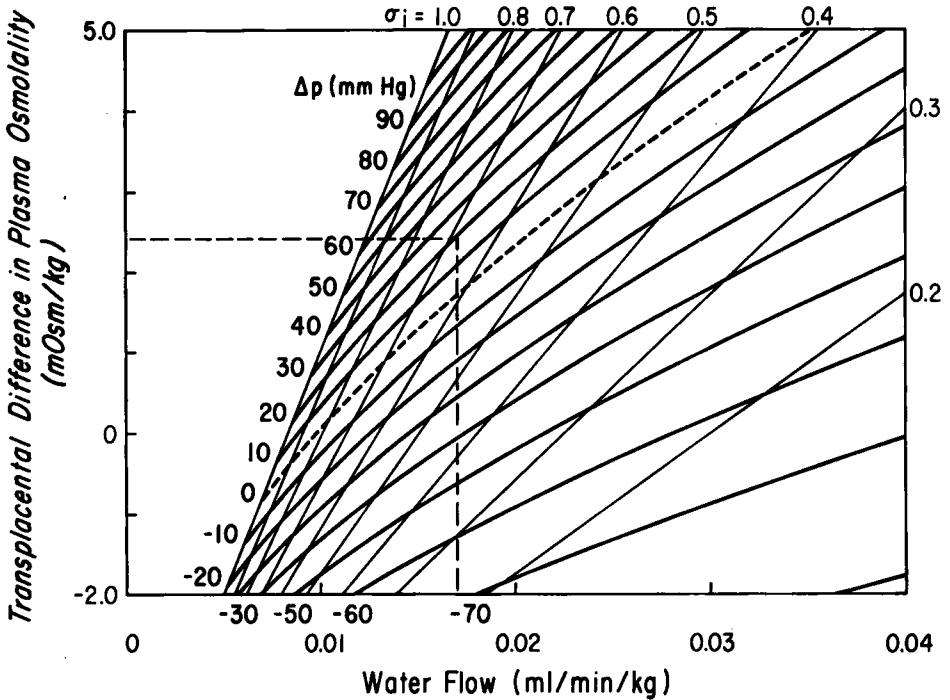


Fig. 1. Equations 1, 2, and 3 were solved for transplacental water flux from mother to fetus and transplacental differences (M-F) in total plasma osmolality. The values substituted into the equations are those of Table 2, except for  $\Delta C_i$ , which was taken as  $\Delta C_{Total} - \Delta C_a$ . The normal values of the transplacental difference in total osmolality (or  $\Delta C_{Total}$ ) and water flux indicate a reflection coefficient of about 0.7 and a hydrostatic pressure difference (M-F) of about 20 mm Hg.

which the fetus can acquire the water and inert solute necessary for its growth. In order to do so, we calculated the value of fetal water influx ( $q_w$ ), which is normally  $1.71 \cdot 10^{-2} \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  ( $= 2.85 \cdot 10^{-4} \text{ ml} \cdot \text{sec}^{-1} \cdot \text{kg}^{-1}$ ) when each of the other variables was varied between 0 and 2 times its normal values. The reflection coefficient was varied between 0 and only 1.47 times its normal value since it can never exceed an absolute value of 1.0. It was assumed that the flux of inert solutes was always proportional to the flux of water, which is equivalent to the assumption that fetal body composition is invariant. The results are shown in Figure 2.

It is apparent that the normal value of the hydraulic conductivity of the membrane ( $L_p S$ ) is ample. Any increase in its magnitude is without physiologic significance. However, a change in the magnitude of the reflection coefficient is a potentially powerful mechanism for changing the rate of fetal water and electrolyte uptake and an increase in the diffusion permeability of inert solutes ( $PS_i$ ) could also be of considerable help. Finally, one sees that the two driving forces

for transfer, the concentration difference of actively transported solutes and the difference in hydrostatic pressure, are relatively powerless regulators in view of the fact that there is no physiologic evidence that the total difference in actively transported solute concentrations increases during gestation and the fact that the difference in hydrostatic pressures may well diminish during this time since fetal arterial blood pressure rises during development. One must conclude therefore, that the most likely mechanism that makes possible the ever increasing rate at which a fetal lamb increases in weight is an increase in the permeability,  $PS_{\text{NaCl}}$  of the placenta of the sheep.

### Confirmatory experiments

The weakness of the analysis is that the calculated permeability parameters are based on mean values for fetal water and inert solute acquisition during gestation. Hence, there is only a single calculated value for

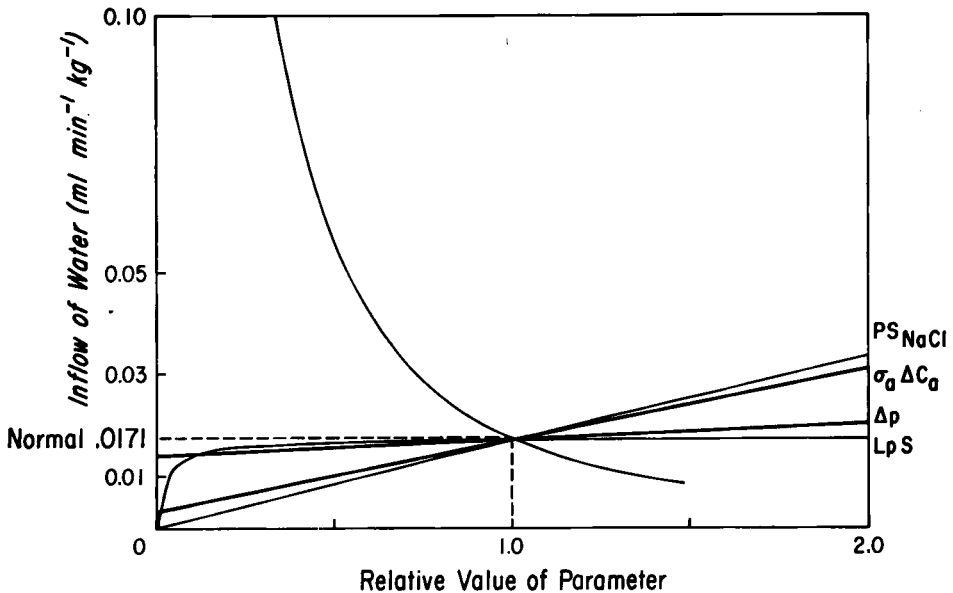


Fig. 2. The influx of water (and accompanying electrolyte) as a function of the membrane parameters of the sheep placenta and some other relevant variables. The relative value of the variables plotted along the abscissa are the values of these variables, divided by their normal value as listed in Table 2.



the parameter  $\sigma_1$  and no measure of its variability.

Recently, we performed long term experiments on fetal lambs with indwelling catheters in whom fetal urine was collected and drained to the exterior. The total volumes collected often far exceeded the total volume of the fetus and its extrafetal fluids. Fetal growth did not appear to be affected. Hence, transplacental fluxes of water and inert solutes were considerably increased; moreover the ratios of inert solute flux and water flux varied from animal to animal. In five animals (11 experiments) mean water flow across the placenta was 8.6 ( $\pm 2.4$  S.D.,  $N = 11$ ) times greater than the normal transplacental water flux and the inert solute flow across the placenta was 3.1 ( $\pm 2.5$  S.D.,  $N = 11$ ) times greater than the normal transplacental inert solute flux. The average of the calculated reflection coefficients  $\sigma_1$  in these 11 experiments was 0.83, with a S.D. of  $\pm 0.18$ , in good agreement with the value originally obtained on the bases of mean transplacental fluxes during normal gestation in the sheep.

## Discussion

These investigations found their origin in the apparent inconsistency that maternal plasma in the sheep is distinctly hyperosmotic with respect to fetal plasma (Meschia *et al.*, 1957; Armentrout *et al.*, 1977) but that water flows from the mother to the fetus. It was observed that whereas the total concentration of inert solutes was higher in the maternal than in the fetal plasma, the total concentration of "active" solutes was higher in the fetal than in the maternal plasma (Armentrout *et al.*, 1977). It appeared possible therefore to explain the osmotic paradox if the "active" solutes are more powerful osmotic agents than the inert solutes. In that case, maternal plasma may be hyperosmotic but at the same time hypotonic with respect to fetal plasma. There may also be an appreciable hydrostatic pressure difference across the placental membrane. The

measurement of the diffusional permeabilities of  $\text{Na}^+$  and  $\text{Cl}^-$  and the measurement of the osmotic filtration coefficient in our laboratory permitted the calculation of all membrane parameters by the additional substitution of the augmented water and salt flows into the transfer equations. From the consistency of the results, we concluded that a filtration diffusion process can account for the fetal acquisition of water and electrolytes in the sheep.

With the values of the membrane parameters in hand, it became possible to compute the placental limitations on fetal growth and to explore new hitherto unsuspected forms of volume regulation. Fetal growth (i.e. water and electrolyte gain) appears to be primarily limited by the electrolyte permeability of the placenta and the prediction that this permeability must increase in the course of gestation in order to make possible the ever increasing rate of fetal weight gain was confirmed by experiment. The salt reflection coefficient was also found to have a profound effect, so much so that it suggested a possible role for vasopressin. Very recent experiments in our laboratory yielded statistically reliable evidence that vasopressin significantly reduces the salt reflection coefficient of the placenta of the sheep and thus makes available to the fetal lamb a short term mechanism by which it can satisfy large increases in its demands for electrolytes and water.

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## Summary

Fetal growth *in utero* demands a continuous flow of water and solutes across the placental barrier. We investigated the membrane parameters that control the influx of solutes that

are not actively transported and the influx of water. The osmotic conductivity, and the  $\text{Na}^+$  and  $\text{Cl}^-$  permeabilities of the membrane were measured in chronically instrumented fetal sheep. Transplacental salt flow and water flow were augmented by drainage of fetal urine to the exterior over extended periods of time. Calculation showed that the membrane parameters are:  $\sigma_{\text{NaCl}} = 0.83$ ,  $P \cdot S_{\text{NaCl}} = 8.0 \cdot 10^{-3} \text{ ml} \cdot \text{sec}^{-1} \text{ kg}^{-1}$ , and  $L_p S = 4.7 \cdot 10^{-8} \text{ cm}^5 \cdot \text{dyne}^{-1} \cdot \text{sec}^{-1} \cdot \text{kg}^{-1}$  (placental surface area  $S$  being expressed per kg fetal weight). The chronic infusion of vasopressin into the fetuses at 8 to 11 units per day per kg fetal weight reduced the reflection coefficient  $\sigma_{\text{NaCl}}$  to a mean of 0.63 ( $P < 0.03$ ). We concluded that the characteristics of the influx of  $\text{NaCl}$  and water are compatible with those of a diffusion filtration process, that fetal growth is constrained by the diffusional permeability of the placenta for inert electrolyte and that in the long run fetal growth can only accelerate because placental electrolyte permeability increases. Vasopressin appears to reduce the salt reflection coefficient of the placenta thus enabling the fetus to exert some short term control over its acquisition of water and electrolyte.

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