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POTENTIAL DIFFERENCES BETWEEN MOTHER AND FOETUS AT DIFFERENT GESTATIONAL AGES IN THE RAT, RABBIT AND GUINEA-PIG

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SUMMARY

1. Potential differences associated with fluid compartments of rat, rabbit and guinea-pig conceptuses have been measured. [Na^+] and [Cl^-] in maternal plasma and amniotic fluid from these three species were also determined.

2. Transplacental potential differences of about 15 mV (foetus positive) were found in the rat, of approximately 0 mV in the rabbit, and of about 18 mV (foetus negative) in the guinea-pig.

3. Amniotic fluid potential differences appeared to arise indirectly from the transplacental potential difference in the rat, from the foetal gastric mucosa in the rabbit, and possibly from the foetal gastric mucosa and indirectly from the placenta in the guinea-pig.

4. The results are discussed in the context of Na^+ transfer to the foetus, and on this basis tend to question the general assumption that almost all Na^+ reaching the foetus passes across the placenta.

INTRODUCTION

An electrical potential difference (p.d.) across a biological membrane arises from a differential passage of ions from one side to the other and in many cases is due to some form of ionic pump deriving its energy from metabolic processes. Observation of p.d.s between maternal tissues and conceptuses of different species, therefore, could yield important information relating to the supply of ions to the foetus. Reports of such p.d.s are restricted to the goat (Meschia, Wolkoff & Barron, 1958), the sheep and cat (Widdas, 1961), the rabbit (Wright, 1963), and the chorioallantoic membrane of the pig (Crawford & McCance, 1960). The object of the present study was to compare the p.d.s associated with the fluid compartments

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of conceptuses from three species with haemochorial placentae, and to assess their possible relevance to foetal Na^+ uptake.

METHODS

Conceptuses from Sprague–Dawley rats, New Zealand White rabbits and mixed strain guinea-pigs, aged from 15 to 22 days, 20 to 30 days, and 35 to 65 days gestational age, respectively, were used. Gestational ages were estimated from known mating dates and according to Huggett & Widdas (1951).

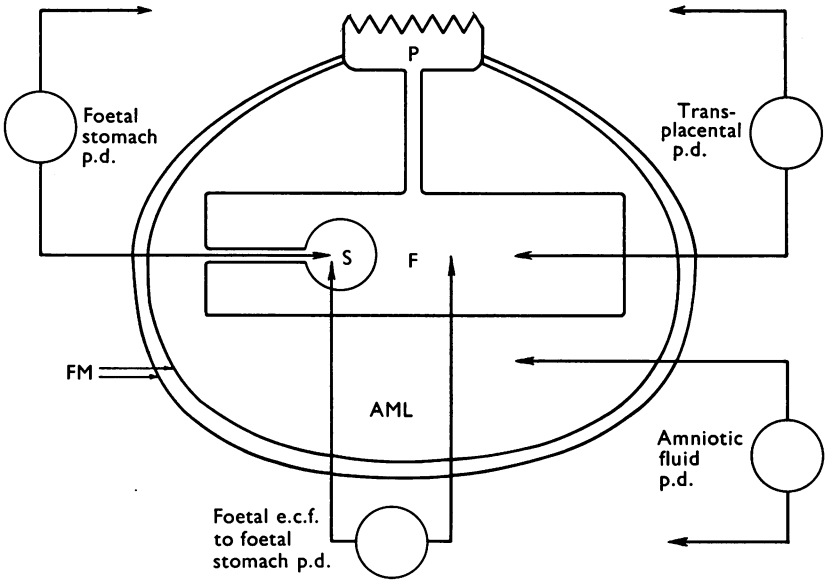

Fig. 1. A schematic representation of the conceptus showing the points between which p.d.s were measured. The diagram shows the foetus (F) bathed in amniotic fluid (AML) which is contained in a sac formed by the placenta (P) and the foetal membranes (FM). The foetal gastric lumen (S) communicates with the amniotic sac via the oesophagus. The whole conceptus is surrounded by uterine tissue which is not shown in this diagram.

Potential difference measurements. All p.d.s were measured using a 'Vibron' electrometer (model 33B E.I.L.), two calomel electrodes and fine polyethylene tubing (o.d. 1·0 mm) containing saturated KCl–2 % agar. Corrections were made for asymmetry.

Terminology. Potential differences measured between the fluid compartments of the conceptus and the maternal extracellular fluid (e.c.f.) will be referred to as the amniotic fluid p.d., the foetal stomach p.d., and the transplacental p.d., and all signs will denote the polarity of the p.d. relative to the maternal e.c.f. (Fig. 1). Potential differences measured between the foetal e.c.f. and the foetal gastric lumen will be referred to as the foetal e.c.f. to foetal stomach p.d., and the sign will show the polarity of the p.d. relative to the foetal e.c.f. (Fig. 1).

Experimental procedure. Rats were anaesthetized with ether, and rabbits and

guinea-pigs with pentobarbitone, 30 mg/kg body weight, given intravenously and intraperitoneally, respectively, and ether. The uterus was exposed by laparotomy.

In vivo *potential difference measurements.* One end of a salt bridge placed in the maternal peritoneal cavity acted as a reference electrode in the maternal e.c.f., and p.d.s were measured between this and one end of a probe salt bridge. Before uterotomy one end of the probe salt bridge was passed through a small puncture in the uterine wall and foetal membranes into the amniotic fluid, then down the oesophagus into the foetal stomach, and finally into the foetal peritoneal cavity by rupturing the stomach wall. This allowed amniotic fluid, foetal stomach, and transplacental p.d. measurements, respectively, to be made. Potential differences were also measured after uterotomy in exposed foetuses with ruptured membranes lying on non-conducting material so that the only contact between mother and foetus was at the placenta. Under these circumstances in the rabbit and guinea-pig, the transplacental p.d. had the same magnitude and sign whether the probe salt bridge was placed in the foetal peritoneal cavity or in the umbilical vein, thus indicating that the p.d. as measured was unaffected by rupturing the stomach wall. The rat umbilical vessels were too small to allow this test to be made, but there was no difference in the magnitude or sign of the transplacental p.d. whether the probe salt bridge entered the foetal peritoneal cavity by rupturing the stomach wall or entered through a small puncture in the abdominal wall. It was not technically possible to use the umbilical vein for transplacental p.d. measurements before uterotomy. In some experiments, usually of longer duration, a terminal decline in the magnitude of the potential differences was observed. In such cases, the p.d.s reported refer to those measured before the condition of the animal deteriorated. The foetuses were weighed within 4 min of being removed from the uterus.

In vitro *potential difference measurements.* Potential difference measurements were performed according to the method of Ussing & Zerahn (1951). Measurements were made across uterine wall and amnion of both rabbits and guinea-pigs, and across the inverted yolk sac splanchnopleur of the rabbit, and the yolk sac splanchnopleur of the guinea-pig. No *in vitro* measurements were made on rat membranes. Intact conceptuses, and pieces of uterine wall overlying them, were removed immediately after uterotomy and placed in Krebs bicarbonate Ringer solution at 4° C. Washed membranes were sandwiched between two Perspex half chambers similar to those designed by Ussing & Zerahn (1951). The effective area of membrane in these chambers was 3·1 cm^2. Solutions on both sides of the membrane were maintained at 30° C, and were stirred and oxygenated by the bubble lift incorporated in the apparatus. All solutions were Krebs bicarbonate Ringer solution, were continuously gassed with a 95 % O_2, 5 % CO_2 mixture, and were at pH 7·4. The Krebs bicarbonate Ringer solution had the following composition (mM): Na^+ 143·2, Cl^- 128·0, K^+ 5·9, Ca^{2+} 2·5, Mg^{2+} 1·1, HCO_3^- 24·9, $H_2PO_4^-$ 1·1, SO_4^{2-} 1·1, glucose 28·0.

Mineral determinations. The [Na^+] in samples of amniotic fluid and maternal plasma, suitably diluted with distilled water, was determined with an atomic absorption spectrophotometer (model SP 90, Unicam Ltd.) and the [Cl^-] was determined with a Technicon Auto Analyser using the standard mercuric thiocyanate–ferric nitrate reaction described by Technicon (method file N-5b).

Estimated values have been expressed in the text as means and standard deviations, with the number of observations in parentheses.

RESULTS

Potential difference measurements

Rats. The results of transplacental p.d. and amniotic fluid p.d. measurements made on seventy-three conceptuses from nine litters ranging from 15 to 22 days gestational age are to be found in Table 1.

Individual transplacental p.d.s both before and after uterotomy were steady, but within each litter values were spread over ranges of up to ± 5 mV. At each gestational age there was no association between

TABLE 1. Transplacental and amniotic fluid potential differences in the rat at different gestational ages

Gestational age (days)	Transplacental p.d. (mV)	Amniotic fluid p.d. (mV)
15	+17 ± 3 (7)	+17 ± 2 (7)
16	+16 ± 4 (9)	+14 ± 4 (9)
17	+15 ± 4 (11)	+15 ± 4 (11)
18	+14 ± 2 (9)	+13 ± 3 (9)
19	+13 ± 4 (8)	+13 ± 3 (8)
20	+15 ± 3 (10)	+14 ± 3 (10)
21	+17 ± 3 (9)	+18 ± 3 (9)
22	+1 ± 2 (5)	+2 ± 3 (5)
22	0 ± 2 (5)	−1 ± 3 (5)

One litter was examined at each age. The results are expressed as means and S.D. with the number of foetuses in parentheses. There was no significant difference ($P > 0{\cdot}1$) between individual transplacental and amniotic fluid p.d.s.

foetal weight and this p.d. Over the age range of 15–21 days the mean transplacental p.d. from each litter showed no gestational age correlation, and the over-all mean was +15 ± 3 mV (63). On the 22nd day of gestation, however, the transplacental p.d. decreased towards 0 mV.

Within individual conceptuses a steady positive amniotic fluid p.d. with a magnitude not significantly different from that of the transplacental p.d. was found at all gestational ages studies. The p.d. was the same whether measured in the amniotic fluid or the foetal buccal cavity.

Rabbits. The results of transplacental p.d., amniotic fluid p.d. and foetal stomach p.d. measurements made on 120 conceptuses from fourteen litters ranging from 20 to 30 days gestational age are to be found in Table 2.

At all ages studied, both before and after uterotomy, transplacental p.d.s of approximately 0 mV were seen. Fluctuations between +2 and −2 mV were frequently observed in individual conceptuses.

A fluctuating negative amniotic fluid p.d. was seen, and within individual litters maximum values were spread over ranges of up to ± 5 mV. Within each litter there was no association between the maximum value of this

p.d. and foetal weight. The mean maximum amniotic fluid p.d. from each litter showed no gestational age correlation, and the over-all mean was -22 ± 5 mV (120). The amniotic fluid p.d. was sometimes steady, but usually fluctuated between -5 to -7 mV and the maximum. It was never seen to increase to 0 mV.

Within individual conceptuses a steady negative foetal stomach p.d. was observed to be usually 5–10 mV more negative than the maximum amniotic fluid p.d. The magnitude of the p.d. was not associated with

TABLE 2. Transplacental, amniotic fluid and foetal stomach potential differences in the rabbit at different gestational ages

Gestational age (days)	Transplacental p.d. (mV)	Maximum amniotic fluid p.d. (mV)	Foetal stomach p.d. (mV)
20	-1 ± 2 (12)	-20 ± 5 (12)	—
21	0 ± 1 (9)	-19 ± 3 (9)	—
21	$+1 \pm 1$ (10)	-30 ± 3 (10)	—
22	0 ± 2 (8)	-14 ± 4 (8)	—
23	0 ± 1 (7)	-29 ± 4 (7)	-34 ± 2 (5)
24	0 ± 2 (10)	-20 ± 2 (10)	-24 ± 3 (7)
25	$+1 \pm 2$ (7)	-27 ± 2 (7)	-30 ± 4 (6)
26	-1 ± 1 (12)	-17 ± 5 (12)	-24 ± 4 (10)
26	$+1 \pm 2$ (7)	-26 ± 2 (7)	-29 ± 3 (5)
27	0 ± 1 (9)	-22 ± 2 (9)	-25 ± 3 (8)
28	-1 ± 2 (8)	-21 ± 2 (8)	-27 ± 2 (8)
29	0 ± 2 (7)	-27 ± 3 (7)	-31 ± 1 (5)
30	0 ± 2 (7)	-24 ± 2 (7)	-26 ± 4 (6)
30	0 ± 1 (7)	-20 ± 2 (7)	-21 ± 2 (7)

One litter was examined at each age. The results are expressed as means and S.D., with the number of foetuses in parentheses.

foetal weight at each gestational age, nor was there any correlation between the mean value for each litter and gestational age. The over-all mean was -27 ± 5 mV (67). The magnitude and sign of the foetal stomach p.d. measured before uterotomy were the same as those of the foetal e.c.f. to foetal stomach p.d. measured after uterotomy.

In vitro no measurable p.d. was detected across the uterine wall, the inverted yolk sac splanchnopleur, or the amnion, either individually or combined, on each successive day between 20 and 30 days gestational age inclusive. Two preparations of each tissue, or combination of tissues, were examined at each age.

Guinea-pigs. The results of transplacental p.d., amniotic fluid p.d. and foetal stomach p.d. measurements made on thirty-five conceptuses from ten litters ranging from 35 to 65 days gestational age are to be found in Table 3.

Negative transplacental p.d.s which were steady were observed in every conceptus. The mean transplacental p.d. from each litter showed no gestational age correlation, and the over-all mean was -18 ± 4 mV (35).

Within individual conceptuses a steady negative amniotic fluid p.d. was seen. This p.d. increased abruptly from a mean value of -50 ± 11 mV (23) before the 60th day of gestation to a mean of -23 ± 4 mV (12) subsequently. At all gestational ages a steady negative foetal stomach p.d. was

TABLE 3. Transplacental, amniotic fluid and foetal stomach potential differences in the guinea-pig at different gestational ages

Gestational age (days)	Number of foetuses	Transplacental p.d. (mV)	Amniotic fluid p.d. (mV)	Foetal stomach p.d. (mV)
35	4	-16 ± 2	-46 ± 7	-48 ± 8
45	3	-16 ± 3	-46 ± 18	-50 ± 18
47	4	-16 ± 3	-58 ± 11	-63 ± 11
50	3	-18 ± 4	-45 ± 6	-48 ± 7
55	3	-25 ± 1	-60 ± 17	-61 ± 17
57	3	-19 ± 7	-51 ± 5	-53 ± 4
59	3	-22 ± 4	-44 ± 7	-51 ± 8
61	4	-16 ± 1	-21 ± 2	-23 ± 1
63	3	-20 ± 1	-19 ± 2	-23 ± 2
65	5	-17 ± 3	-27 ± 2	-30 ± 3

One litter was examined at each gestational age. The results are expressed as means and S.D. There was no significant difference ($P > 0{\cdot}1$) between the magnitudes of the amniotic fluid and foetal stomach p.d.s.

found to be usually between 2 and 7 mV more negative than the amniotic fluid p.d., but its magnitude was not significantly different from that of the amniotic fluid p.d.

In vitro no measurable p.d. was detected across the uterine wall, the yolk sac splanchnopleur, or the amnion, either individually or combined, at each of 30, 40, 50, 55, 60 and 65 days gestational age. Two preparations of each tissue or combination of tissues were examined at each age.

Sodium and chloride determinations

In all cases the $[Na^+]$ and $[Cl^-]$ of maternal plasma were compared with those of amniotic fluid, and the results are given in Table 4. Amniotic fluid from each foetus was pooled to give a representative sample from each litter.

There was no correlation between gestational ages and $[Na^+]$, or $[Cl^-]$, in either of the two fluids in any of the species. However, the $[Na^+]$ of amniotic fluid was significantly less than that of maternal plasma in all

three species, and in the guinea-pig the amniotic fluid [Cl^-] was significantly greater than that of maternal plasma.

A comparison of the observed amniotic fluid/maternal plasma [Na^+], and [Cl^-] ratios, and those calculated on the assumption that these ions are distributed according to electrochemical equilibrium, is presented in Table 5.

TABLE 4. The [Na^+] and [Cl^-] of maternal plasma and amniotic fluid from rats, rabbits and guinea-pigs

		Maternal plasma		Amniotic fluid	
Species	Gestational age range (days)	[Na^+] (m-equiv/l.)	[Cl^-] (m-equiv/l.)	[Na^+] (m-equiv/l.)	[Cl^-] (m-equiv/l.)
Rat (5)	16–20	152 ± 5	103 ± 2	133 ± 5***	105 ± 4
Rabbit (11)	20–30	155 ± 5	103 ± 5	138 ± 12***	107 ± 5
Guinea-pig (6)	30–65	145 ± 4	97 ± 2	134 ± 8**	140 ± 15***

The results are expressed as means and S.D. with the number of animals in parentheses. Starred values are significantly different (*** = $P < 0{\cdot}001$; ** = $0{\cdot}01 > P > 0{\cdot}001$) from those of the maternal plasma.

TABLE 5. The observed amniotic fluid/maternal plasma [Na^+] and [Cl^-], ratios, and those calculated assuming distribution of these ions according to electrochemical equilibrium

	Amniotic fluid/maternal plasma ratio			
	[Na^+]		[Cl^-]	
Species	Observed	Calculated	Observed	Calculated
Rat	0·88	0·57	1·02	1·75
Rabbit	0·89	1·41	1·04	0·71
Guinea-pig	0·92	6·25	1·44	0·16

The observed ratios are derived from the data summarized in Table 4. The calculated ratios are derived from the relevant mean maternal plasma concentration (Table 4) and the observed mean amniotic fluid p.d.s; in the rat +15 mV, in the rabbit −5 and −22 mV, and in the guinea-pig −50 mV. The calculated ratio for each ion in the rabbit is the mean of the ratio obtained using −5 mV and that obtained using −22 mV as the amniotic fluid p.d.

In the three species it appears that the distribution of Na^+ between maternal plasma and amniotic fluid is not according to electrochemical equilibrium, since in the rat the observed amniotic fluid [Na^+] is greater than the calculated value, and in the rabbit and guinea-pig, the observed concentration is less than the calculated value. In the rat, therefore, it seems that Na^+ being driven by the electrochemical gradient would tend

to diffuse out of the amniotic fluid against its concentration gradient. In the rabbit and guinea-pig, it appears that both the concentration and the electrochemical gradient would tend to favour diffusion of Na^+ from the maternal plasma into the amniotic fluid.

The observed amniotic fluid [Cl^-] is less in the rat, and greater in the rabbit and guinea-pig, than the values calculated on the assumption that Cl^- is distributed according to electrochemical equilibrium.

DISCUSSION

In the rat the magnitude and sign of the transplacental p.d. were the same both before and after uterotomy. Since the foetal trophoblasts of haemochorial placentae are bathed directly in the maternal blood, the site of origin of these potential differences thus appears to have been the foetal placenta. However, it is not possible from these results to establish the location and nature of the (active) mechanisms producing the transplacental p.d. with greater precision.

That the transplacental p.d. and the amniotic fluid p.d. have the same magnitude and sign suggests that there is no specific (active) mechanism directly producing the amniotic fluid p.d. This p.d. may arise indirectly from the transplacental p.d. by a relatively free exchange of ions between the amniotic fluid and the foetal blood at the surface of the yolk sac splanchnopleur, or in the foetal stomach, or both.

In the rabbit the site of origin of the amniotic fluid p.d. does not seem to be the uterine wall, the inverted yolk sac splanchnopleur, or the amnion, since they display no spontaneous electrical activity *in vitro*. This confirms previous *in vitro* observations on rabbit amnion (Wright, 1963). The foetal gastric mucosa, however, appears to be a source of electromotive force *in vitro*, the mucosal side being negative (Wright, 1962), and it has been suggested that this is the site of origin of the amniotic fluid p.d. (Wright, 1963). It has also been suggested that the fluctuations in the amniotic fluid p.d. are due to sphincter activity associated with swallowing, since such activity would cause changes in the potential drop occurring between the foetal stomach and the amniotic fluid (Wright, 1963). The *in vivo* and *in vitro* results presented here are in complete agreement with these hypotheses.

In order to account for the difference between the steady foetal stomach p.d. and the maximum amniotic fluid p.d. Wright (1963) postulated a positive transplacental p.d. He was, however, unable to detect such a p.d., and this was also the case in the more extensive study presented here. A transplacental p.d. would necessarily have the same magnitude as the difference between the foetal stomach p.d. and the foetal e.c.f. to foetal

stomach p.d. Since no such difference was found it can be concluded that there is no transplacental p.d. in the rabbit.

In the guinea-pig, as in the rat, the site of origin of the transplacental p.d. appears to be the foetal placenta, although the precise location and nature of the (active) mechanisms remain unestablished. The negative polarity in this case indicates that the mechanism is different from that of the rat, and an inverse orientation of a cation pump directed towards the maternal blood, or an anion pump towards the foetal blood, or both, would need to be postulated.

The amniotic fluid p.d. of the guinea-pig does not appear to originate from the uterine wall, the yolk sac splanchnopleur, or the amnion, since no electrical activity is associated with these tissues *in vitro*. The presence of a foetal stomach p.d. suggests, therefore, that the foetal gastric mucosa is a source of electromotive force contributing to the amniotic fluid p.d., in addition to the contribution from the transplacental p.d.

Enders (1967) demonstrated that haemochorial placentae could be subdivided into several groups on the basis of trophoblastic layering. It appears that the rat has a three-layered trophoblast (haemotrichorial), the rabbit two layers (haemodichorial), and the guinea-pig one layer (labyrinthine haemomonochorial). The transplacental p.d. of the rat is positive, there is no such p.d. in the rabbit, and this p.d. in the guinea-pig is negative. Whether the species differences in these transplacental p.d.s are associated with the trophoblastic layering is uncertain, but it can be stated with confidence that each of these three placentae is anatomically and physiologically distinct.

It is of interest that the type of transplacental p.d. observed seems to correlate with the physiological maturity of the foetuses at birth, since the rat foetus is the least mature, the rabbit is intermediate, and the guinea-pig is the most mature. However, the significance of this is unknown.

Net flux of Na^+ towards the foetus, which equals the rate of foetal Na^+ retention, is far exceeded by the total flux of Na^+ towards the foetus (Flexner & Pohl, 1941*a*, *b*, *c*). If the positive transplacental p.d. in the rat is due to active Na^+ transport, net Na^+ flux across the placenta will be towards the foetus. This is suggested by the close correlation between the decline towards 0 mV of this p.d. on the 22nd day, and an abrupt decrease on the 22nd day in the total flux of Na^+ towards the foetus (Flexner & Pohl, 1941*a*). Following this decline, Na^+ enters the foetus at about 45% of its entry rate on the 21st day. The fall in the p.d. could be due to either a failure of the cation pump mechanism or a large increase in ionic permeabilities which results in the electrogenic ion pump being short-circuited. The above observations would favour the former explanation.

The absence of a transplacental p.d. in the rabbit is consistent with the

suggestion of Faber & Hart (1967) and Faber, Hart & Poutala (1968) that Na^+ and Cl^- cross the placenta by passive diffusion. It is of interest that on about the 28th day of gestation passive Na^+ exchange between the maternal and foetal blood streams in the placenta, which occurs at a rate of approximately 0·014 m-equiv/min (Faber & Hart, 1967), only accounts for 55–65 % of the total flux of Na^+ towards the foetus in the intact animal (Flexner & Pohl, 1941*b*). It may be, therefore, that the placenta is not the only path by which Na^+ may reach the foetus. Na^+ is actively transported from the mucosal to the serosal surface of the foetal stomach (Wright, 1962). The negative foetal stomach p.d. may arise from this active Na^+ absorption, and after the 23rd day of gestation, from active Cl^- secretion (accompanied by H^+) into the gastric lumen (Wright, 1962). It seems reasonable to suggest that this activity of the foetal gastric mucosa is responsible for the observed amniotic fluid [Na^+] being lower, and the [Cl^-] being higher, than the values expected under conditions of electrochemical equilibrium (Table 5). It appears, therefore, that if Na^+ can reach the amniotic fluid by diffusion down the concentration and the electrochemical gradient from the maternal circulation and, after being swallowed, is actively absorbed from the foetal gastric lumen, this would produce a net flux towards the foetus. If this were to exceed Na^+ requirements, net Na^+ flux along at least one other transfer path would be towards the mother.

If the negative transplacental p.d. in the guinea-pig is due to active Na^+ transport, net Na^+ flux across the placenta would need to be from foetal to maternal blood. Since foetal Na^+ requirements are met, such a loss would need to be made good or exceeded by net Na^+ flux towards the foetus along other transfer paths. One of these paths may involve transfer from maternal blood to the amniotic fluid, followed by active absorption of Na^+ from the foetal gastric lumen, as in the rabbit. Indeed, the negative foetal stomach p.d., the lower amniotic fluid [Na^+] and the higher [Cl^-] (Table 5) suggests similar gastric mucosal activity in the guinea-pig foetus, and this appears to be worthy of further study.

However, the over-all negativity of the guinea-pig foetus relative to maternal blood, coupled with the fact that Na^+ requirements are actually met in the intact animal, suggests that the driving force arises either from an anion pump or a neutral sodium chloride pump followed by Na^+ reabsorption. The total flux of Na^+ as measured by Flexner & Pohl (1941*c*) may have arisen from fluxes towards the foetus along several routes. The distinct differences in the p.d.s shown in these three species thus call in question the general assumption that transfer of Na^+ towards the foetus results almost entirely from transplacental passage from mother to foetus.

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