The Role of the Fetal Hypothalamus in Development of the Feto-Placental Unit and in Parturition

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INTRODUCTION

Fetal growth is known to be influenced by many maternal and environmental factors (e.g. Knobil and Caton, 1953; Gruenwald, 1966; Kloosterman, 1966; Thomson *et al.*, 1968; Hoet, 1969). Moreover, maternal neuroendocrine factors are supposed to be involved in the initiation of parturition (Lincoln, 1971, 1974; Swaab, 1972).

Recent studies indicate that the fetal brain also plays an active role in fetal body and placental growth (Honnebier and Swaab, 1973a; Swaab and Honnebier, 1973). In addition, the fetus is considered to be involved in the timing of the onset of delivery (Liggins *et al.*, 1967; Liggins, 1968, 1969; Chard *et al.*, 1970).

The present paper will review the experimental and clinical basis for the assumption of an active role of the fetal hypothalamus in intrauterine growth and parturition.

INFLUENCE OF FETAL BRAIN LESIONS UPON DEVELOPMENT OF THE FETO-PLACENTAL UNIT

In order to study the influence of the fetal brain on intrauterine growth of the fetus and the placenta, various experimental techniques (see below) have been applied to eliminate the fetal brain or the fetal hypophysis. Observations on human anencephalics were also considered for this purpose since the hypothalamus is either missing or grossly disturbed in this condition (Tuchmann-Duplessis and Gabe, 1960; Eguchi, 1969; Grumbach and Kaplan, 1973).

Influence upon fetal growth

In mice, fetal body growth was inhibited after X-ray destruction of the fetal hypophyseal area (Raynaud, 1950).

In rat, reduction in the average body weight after fetal decapitation was reported to be 5–15% (Jost, 1966a) or 20% (Heggstad and Wells, 1965). A reduction in body weight of 12% (Fujita *et al.*, 1970) or 22% (Swaab and Honnebier, 1973) was observed after electrocoagulation of the fetal hypothalamus or brain respectively, while

7% reduction was observed after compression of the fetal rat brain (Fujita *et al.*, 1970). We used a simple technique in removing fetal rat brain by aspiration. This procedure appeared to have various advantages over fetal decapitation. By means of this procedure a reduction of 25–33% of the fetal body weight was observed (Swaab and Honnebier, 1973). Since reduction of fetal body weight has been reported after destroying the hypothalamus, but not after destroying other brain areas (Fujita *et al.*, 1970), the primary cause of this growth reduction is likely to be situated in or near the hypothalamus.

Decapitation of fetal mice (Eguchi, 1961) and rabbits (Jost, 1966a) did not cause any growth inhibition. Important for the interpretation of the difference between these results and our data except for possible species differences, however, is the fact that with our procedure all the fetuses in a litter are brainless. This excludes the possibility

TABLE I

EARLY GROWTH INHIBITION IN PREGNANCIES WITH ANENCEPHALY

Moment at which the uterine size was considered to be too small for gestation length in records of pregnancies with anencephaly, described by Honnebier and Swaab (1973a) and in one patient (*) sent to us by Dr. W. H. M. van der Velden (see Honnebier *et al.*, 1974).

<i>Gestation length (in weeks) that uterus was found to be too small for date for the first time</i>	<i>Estimated uterine size (in weeks) at that moment</i>	<i>Gestation length at which parturition took place (weeks)</i>
13	12	40
13	12	38
15	12	44
15	10–12	33
16	14	37
17	15	35
18	16	31
18	14	39
19	18	42
20*	18*	35*
20	18	41
20	18	36
22	20	34
23	22	37
24	23	43
24	22	46
25	22	33
26	22	51
26	25	34
26	24	47
26	24	52
28	24	43
29	26	36
29	27	43
34	32	45

of the transfer of substances from the fetal brain or hypophysis of unoperated litter-mates to the operated fetuses via the maternal circulation.

In sheep, coagulation of the fetal hypophyseal area inhibited fetal body growth and bone-age development (Liggins and Kennedy, 1968). A decreased birth weight was also observed after fetal decapitation in sheep (Lanman and Schaffer, 1968) and in Guernsey calf fetuses suffering from an inherited adeno-hypophyseal aplasia (Kennedy *et al.*, 1957). Even after prolonged gestation this last malformed fetus is reported to remain small and to have a premature appearance (Kennedy *et al.*, 1957).

Hutchinson *et al.* (1962) do not give sufficiently exact data to judge the existence of an effect of fetal hypophysectomy upon intrauterine growth in monkey.

A reduced growth exists in human anencephalics (Hoet, 1969; Milic and Adamsons, 1969; Kučera and Doležalová, 1972; Honnebier and Swaab, 1973a). The average ponderal growth of anencephalics was estimated to be 97 g/week against 143 g/week in controls. The anencephalics reached therefore only far beyond 40 weeks the birth weight of the control group at term (Honnebier and Swaab, 1973a).

Our data on anencephalic birth weights (Honnebier and Swaab, 1973a) start at 28 weeks of pregnancy. Clinical observations on these patients indicate, however, that growth retardation starts already much earlier (Table I).

However, other serious congenital malformations are also reported to have lower birth weights (Battaglia, 1970; Kučera and Doležalová, 1972; Schutt, 1965). Therefore the data of our anencephalic group were compared with those of children having other kinds of serious congenital malformations (Table II). Birth weight of anencephalic children appeared to be definitely less than that of the group with other congenital anomalies (Fig. 1).

TABLE II

CONGENITAL ANOMALIES DESCRIBED IN FIGS. 1, 2, 3

Congenital anomalies of the children presented in Figs. 1, 2 and 3. Classification according to: International statistical classification of diseases, injuries and causes of death 1965, detailed list (three-digit categories, see C. B. S., 1972).

<i>Classification</i>	<i>Number</i>
745; Cong. anom. of ear, face and neck	2
746; Cong. anom. of heart	26
748; Cong. anom. of respiratory system	1
750; Other cong. anom. of upper alimentary tract	17
751; Other cong. anom. of digestive system	11
753; Cong. anom. of urinary system	29
755; Other cong. anom. of limbs	1
756; Other cong. anom. of musculoskeletal system	9
757; Cong. anom. of skin, hair and nails	2
758; Other and unspecified cong. anom.	2
759; Cong. syndromes affecting multiple systems	11
Total	111

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Twin pregnancies, discordant for anencephaly, show that the decreased birth weight in anencephaly is not caused by an alteration in maternal environment (Honnebier and Swaab, 1973a).

Children with a congenital aplasia of the hypophysis are reported to have normal

Fig. 1

Fig. 2

Fig. 3

Figs. 1-3. The distribution of birth weight, placental weight and placental index over the centile groups of the controls is shown in Figs. 1, 2 and 3 respectively. The data of the "normal" group obtained by Kloosterman (1970) are compared with those of 122 anencephalics (Honnebier and Swaab, 1973a) and 111 children with serious congenital anomalies (except for anencephaly) (for details see Honnebier and Swaab, 1973a). The anencephalic birth weights have been corrected approximately for their absence of brain weight. Appropriate brain weights according to gestation length were obtained by interpolation using the data of Gruenwald (1963) and Blinkov and Glezer (1968). These brain weights were added to the birth weights of the anencephalic children. The group of children having other serious congenital anomalies was collected out of the 147 children dying perinatally between 1948 and 1957 in the Training School for Midwives in Amsterdam, and between 1958 and 1971 in the Department of Obstetrics and Gynaecology, University of Amsterdam. From this group 36 children were excluded which had congenital anomalies of the central nervous system (22 cases of congenital hydrocephalus (category according to C.B.S., 1972: 742), 1 case of spina bifida (category: 741) and 13 other congenital anomalies of the nervous system (category: 743)). The distribution of the remaining 111 children over the various categories is given in Table II. From the distribution of the data over the centile groups and the place of the median (vertical lines, calculated according to De Jonge, 1963, chapt. 2.2.2.), it appears that the correlated anencephalics show a lower birth weight and placental weight and a higher placental index (as compared to the normal group as well as to the group having congenital anomalies). The group with congenital malformations shows birth and placental weights lying in between the normal group and the anencephalics, while its placental index was less than that of the control group.

birth weights (Table III). The primary cause of the reduced growth in anencephalics is therefore likely to be situated at the level of the hypothalamus. This relative unimportance of the presence of the hypophysis for the stimulation of intrauterine growth is supported by the data on anencephalics (see above) and by the work of Dupouy and Jost (1970) who observed an even greater decrease in body weight in encephalectomized rats that have a hypophysis than in decapitated animals.

TABLE III
CHILDREN WITH PITUITARY APLASIA

<i>Literature reference</i>	<i>Gestation length (weeks)</i>	<i>Sex</i>	<i>Birth weight (g)</i>	<i>Pituitary</i>	<i>Age at death</i>
Blizzard and Alberts (1956)	40	♂	4400 97.7-100 centile*	No adenohypophysis No pituitary stalk No neurohypophysis	18 h
Brewer (1957)	34.5	♀	1970 10-25 centile	No adenohypophysis Normal neurohypophysis	4.75 h
Reid (1960)	40	♂	4050 90-95 centile	No adenohypophysis No neurohypophysis No pituitary stalk	19 h
Dunn (1966)	44	♀	5464 97.7-100 centile	Only neurohypophyseal tissue	18 h
Johnson <i>et al.</i> (1973)	41.5	♀	3400 25-50 centile	No adenohypophysis Small neurohypophysis	21 days

* According to Kloosterman (1970).

Influence upon placental growth

A strongly positive relation seems to exist between placental and fetal weight (Kloosterman and Huidekoper, 1954; Dawes, 1968; Solomon and Friesen, 1968). Removal or destruction of a part of the placenta reduces fetal growth (Dawes, 1968; Gammal, 1973), while removal of the fetus inhibits placental growth (Van Wagenen and Catchpole, 1965).

In rat, placental weight decreased after aspiration of the fetal brain, while the placental index (*i.e.* placental weight divided by fetal weight) appeared to be increased (Swaab and Honnebier, 1973).

In sheep, microscopical placental changes were reported after fetal hypophysectomy (Liggins and Kennedy, 1968); placental weights were unfortunately not mentioned.

In human anencephalics a decreased placental weight and increased placental index were also observed (Milic and Adamsons, 1969; Honnebier and Swaab, 1973a). Reduction in placental weight of anencephalics appeared to be much more pronounced than that of other congenital anomalies (Fig. 2). The placental index of the last group is even less than in the controls while in the anencephalics it is increased (Fig. 3).

INFLUENCE OF HYPOPHYSEAL HORMONES AND OTHER COMPOUNDS UPON
DEVELOPMENT OF THE FETO-PLACENTAL UNIT

As has been mentioned before, destruction of the fetal brain or hypophyseal area induces growth retardation of the fetus and of the placenta in various species. In order to determine factors responsible for these inhibitions, the influence of some hypophyseal compounds, brain extracts and insulin on intrauterine development were determined, and are discussed in the following paragraphs.

Growth hormone

Growth hormone has been demonstrated in the fetal pituitary of various species (Bassett *et al.*, 1970; Franchimont, 1971; Grumbach and Kaplan, 1973) as well as in the fetal circulation (Bassett *et al.*, 1970). Although rat plasma growth hormone decreases after encephalectomy and disappears after decapitation (Jost *et al.*, 1974), and is lower in anencephalics than in normal newborns (Grumbach and Kaplan, 1973) the role of this hormone in fetal growth seems, however, not to be important.

Placental transfer of growth hormone is supposed to be unimportant (Jost and Picon, 1970; Bassett *et al.*, 1970), yet effects were observed in the fetus after administration of the hormone to the mother. Administration of crude growth hormone preparations (Phylol, Antuitrin-G) to the mother rat induced in some groups a slight increase in full term body weight (Hultquist and Engfeldt, 1949), while pure growth hormone induced in some groups a slight increase—but in other groups even a decrease—in body weight (Engfeldt and Hultquist, 1953). Literature data about these experiments are difficult to interpret because of the possible effects of impurities in

the crude growth hormone preparations that were used. This problem is illustrated by the fact that Zamenhof *et al.* (1966) could not find an increased fetal body weight after either s.c. or i.v. administration of NIH-growth hormone (3 mg/day) to the mother, although a pronounced increase in fetal brain weight was observed.

Administration of growth hormone directly to the fetus failed to give clear-cut results. That administration of bovine growth hormone to decapitated rats should increase fetal weight cannot be maintained, since only 5 experimental fetuses were studied (Heggestad and Wells, 1965). In addition, we were unable to confirm this growth promoting effect (Tables VI, VII). Also our preliminary studies in brain-aspirated fetuses, injecting 10 μ g NIH-GH-S 9 (ovine) in 50 μ l 0.9% NaCl and 10 μ g or 50 μ g of this hormone in 50 μ l oleum rapae per fetus, were negative in this respect. In decapitated rabbit fetuses, only a trend towards increase in size was observed after growth hormone administration (Jost, 1966a). Injection of growth hormone into the intact rat fetus gave either slightly decreased birth weights (Hwang and Wells, 1959; Heggestad and Wells, 1965) or no effect at all (Table VII).

There is also no clinical evidence at present for a role of growth hormone in human fetal growth. Congenital aplasia of the fetal pituitary goes together with normal birth weight (Table II). In addition, ateleotic dwarfs (McKusick and Rimoin, 1967; Rimoin *et al.*, 1966a, b) and acromegalic women usually have children with normal birth weights (Solomon and Friesen, 1968; Hoet, 1969). In addition, no relation was found between maternal growth hormone levels and birth weight (Parekh *et al.*, 1973), while even a negative relation exists between fetal growth hormone levels and birth weight after 20–21 weeks of pregnancy (Cramer *et al.*, 1971; Kaplan *et al.*, 1972).

A remarkable increase in placental weight was found after growth hormone injection into brain-aspirated fetuses (Table VIII) as well as into intact ones (Table IX). This effect was also obtained by administration of cyclic-AMP (Table VIII) to brain-aspirated fetuses. The latter observation and the finding that this effect could not be obtained in intact fetuses cannot be interpreted in the present stage of the study. The lower placental weights found in brain-aspirated fetuses (Swaab and Honnebier, 1973) and in anencephalic infants (Honnebier and Swaab, 1973a), together with the heavier placentas after growth hormone treatment, suggest that growth hormone may play a role in the development of the placenta. Also interesting in this respect is the trend towards heavier placentas found after growth hormone administration to pregnant rats (Croskery *et al.*, 1973).

Adrenocorticotrophic hormone (ACTH)

The fetal adrenal has been shown to be stimulated by the fetal hypothalamo-hypophyseal system in man, as well as in various animals (Jost, 1966b; Jost *et al.*, 1970; Honnebier *et al.*, 1974). ACTH that has been identified in sheep fetal pituitaries and blood (Alexander *et al.*, 1973) does not pass the placenta (Alexander *et al.*, 1971; Honnebier *et al.*, 1974). Transplacental passage of adrenal steroids does take place, however (Angervall and Martinsson, 1969; Jost and Picon, 1970).

Corticotropin administration to pregnant rats was found to decrease fetal body

weight (Hultquist and Engfeldt, 1949; Noumura, 1959). Although cortisone injection in the pregnant mother rat has been reported to increase fetal growth (Angervall and Martinsson, 1969), others found a slight decrease in fetal growth (Noumura,

Fig. 4. Stimulation of fetal adrenal size by ACTH. For description of the experimental procedure and the Sudan-black-B staining of the sections, see legend of Table IV. Left: control adrenal (brain-aspirated fetus receiving 0.9% NaCl); right: ACTH-stimulated adrenal (brain-aspirated fetus receiving ACTH).

1959). Moreover, injections of corticotropins as well as of adrenal steroids into intact and decapitated fetuses were reported to inhibit fetal growth (Noumura, 1959; Kitchell and Wells, 1952). In brain-aspirated fetuses a wide lipid-free layer was found in the outer zone of the adrenals (Fig. 4), that has also been described after fetal decapitation (Noumura, 1959). After ACTH treatment (Cortrosyn-depot[®]) this outer zone of the adrenals also contained lipids (Fig. 4). Adrenal length and width were 32% and 42% enlarged respectively (Table IV). Neither body weight nor placental weight could however be restored, either by short- or by long-acting ACTH (Tables VI, VIII).

Since also in humans, birth weight of children with congenital adrenal hyperplasia (Price *et al.*, 1971) and hypoplasia (O'Donohoe and Holland, 1968) is normal, the fetal adrenal cannot be important for fetal growth.

TABLE IV

EFFECT OF ACTH ADMINISTRATION TO BRAINLESS FETUSES ON FETAL ADRENAL SIZE

In the present experiment, the 5 control and 5 Cortrosyn-depot treated animals of Table VI were studied. The adrenals of the two fetuses situated at the ovarian ends of the left uterine horns were frozen in liquid-nitrogen-cooled Freon-12. Serial sections (16 μ m) were made on a cryostat. The sections were post-fixed in an ethanol-formalin-acetic acid mixture and alternately stained by means of thionin (Windle *et al.*, 1943) or Sudan-black-B (Noumura, 1959). Of each fetal adrenal the largest diameter ("length") and the diameter perpendicular to this ("width") were measured under a microscope. The increase in length as well as in width after ACTH administration is highly significant (Student *t*-test: $P < 0.001$; De Jonge, 1963, chapt. 13).

	<i>Control fetuses</i>	<i>ACTH treated fetuses</i>
Treatment of the fetus	Brain aspiration day 19 and administration of 50 μ l 0.9% NaCl s.c. to the fetus.	Brain aspiration day 19 and administration of 50 μ l Cortrosyn-depot [®] s.c. to the fetus.
Adrenal length (in mm)	1.34 (S.E.M. 0.030)	1.77 (S.E.M. 0.024)
Adrenal width (in mm)	0.95 (S.E.M. 0.042)	1.35 (S.E.M. 0.060)

Thyreotropic hormone (TSH)

The rat fetal thyroid is regulated near term by the fetal pituitary (Jost, 1966a; Jost *et al.*, 1970). TSH has been identified in the fetal pituitary (Conklin *et al.*, 1973) and serum (Erenberg and Fisher, 1973). TSH is not supposed to pass the placenta (Kajihara *et al.*, 1972; Furth and Pagliara, 1971; Knobil and Josimovich, 1959; Jost *et al.*, 1974). In contrast, TSH-RF (Kajihara *et al.*, 1972; D'Angelo and Wall, 1972), iodine and some organic iodine-containing compounds cross the placenta readily (Furth and Pagliara, 1971). Administration of thyreotropic hormone to the pregnant mother rat (Hultquist and Engfeldt, 1949) was found to reduce fetal body weight slightly.

Hopkins and Thorburn (1972) observed a decreased body weight and bone-age in athyroid lambs. In addition, the same phenomenon was seen in fetal lambs from ewes given methylthiouracil (Lascelles and Setchell, 1959). These experiments indicate a role of TSH in fetal growth in sheep. Thyroidectomized rabbit fetuses, however, did not show any significant reduction in fetal weight (Jost, 1971). Moreover, no increase in fetal body weight was observed after administration of TSH or thyroid hormones to the rat fetus (Hwang and Wells, 1959; the present study: Table VI). No positive relation exists between thyroid weight and body weight in rat fetuses (Angervall and Lundin, 1963). Also the placental weight was not found to change after TSH administration (Table VIII).

As congenital hypothyroidism is reported to be accompanied by normal birth weight

(Page, 1969; Paine, 1971), also in the human the thyroid does not seem to be important for intrauterine growth.

Gonadotropic hormones

Gonadotropic hormones are present in the fetal pituitary (Jost, 1966a; Ingleton *et al.*, 1971; Grumbach and Kaplan, 1973) and in the fetal circulation (Levina, 1972; Grumbach and Kaplan, 1973). Prolactin (Delost, 1971), LH (Foster *et al.*, 1972) and HCG (Honnebier *et al.*, 1974) were found not to cross the placenta.

Prolactin (Delost, 1971), chorionic gonadotropins and PMS gonadotropins (Hultquist and Engfeldt, 1949), injected into pregnant animals, did not influence fetal body weight. Prolactin administration to intact mouse fetuses (Jean and Delost, 1969) and prolactin, LH or FSH to brain-aspirated rat fetuses (Table VI) did not change either fetal body weight or placental weight (Table VIII). Furthermore, after chorionic gonadotropins or PMS given to decapitated or intact rat fetuses (Noumura, 1959) or HCG administration to brain-aspirated fetuses (Table VI) no increase in body weight was observed. Administration of chorionic gonadotropins to the fetuses did not change placental weight (Table VIII). Gonadotropic hormones thus do not have any stimulating effect on intrauterine growth.

Sex hormones, *i.e.* estrogens (Delost, 1971; Kitchell and Wells, 1952; Noumura, 1959), testosterone (Noumura, 1959), progesterone (Kitchell and Wells, 1952), administered to the rat fetus, or testosterone-propionate (Slob, 1972), androstenediol-dipropionate, methyl-androstenediol-dipropionate (Jost, 1954), administered to the mother failed to increase fetal body weight. Moreover, injection of a progesterone-estrogen combination into intact pregnant rabbit fetuses does not influence placental weight (Butterstein and Leathem, 1970). And so neither gonadotropic hormones nor sex hormones stimulate intrauterine growth.

Posterior and intermediate lobe hormones

Vasopressin, oxytocin and neurophysins are present in the fetal hypothalamo-neurohypophyseal system (HNS) (Dicker and Tyler, 1953; Roffi, 1958; Alexander *et al.*, 1973). In addition, these hormones have been found in the fetal blood (Alexander *et al.*, 1973; Chard, 1972; Edwards, 1971; Robinson *et al.*, 1971).

No difference in pup weight was observed in Brattleboro rats being homozygous or heterozygous for hypothalamic diabetes insipidus (Boer *et al.*, 1974). Therefore, a lack of active maternal and fetal vasopressin does not influence fetal growth. This agrees with the results of two sets of preliminary experiments (Swaab and Veerkamp, unpublished data) in which vasopressin was administered to pregnant rats (Table V). Parturition occurred in all these groups within the same period. As is shown in Table V, vasopressin treatment of the mother did not increase pup weight.

During the administration of oxytocin to the litter, the uterus became clearly pale and contracted. However, the litters were not born before the day of weighing (*i.e.* day 21). Oxytocin (Piton-S) slightly decreased the weight of the brain-aspirated fetuses

TABLE V

INFLUENCE ON PUP WEIGHT OF VASOPRESSIN ADMINISTRATION TO THE MOTHER

Pregnant rats obtained the following treatments from day 7 of pregnancy (the day that spermatozoa were found in the vaginal smear being taken as day 0). Ia: 9 controls were injected with arachnoid oil in the same volume as the experimental rats. Ib: 9 rats obtained vasopressin (Pitressin tannate in oil, Parke-Davis, 5 pressor units/ml) in a dose of 1 I.U. daily from day 7 of pregnancy and of 2 I.U. daily from day 14 of pregnancy. Ic: 7 rats were given the same treatment as in b, but the drinking water contained 1% NaCl. IIa: 7 controls obtained a treatment as in Ia. IIb: 4 animals were given vasopressin in a dose of 5 I.U. daily from day 7.

Group	Number of mothers	Mean number of pups per litter	Weight of the whole litter (g)	Mean body weight per pup (g)
Ia	9	11.3	59.5	5.3
Ib	9	11.4	57.7	5.0
Ic	7	11.7	60.7	5.2
IIa	7	11.1	59.4	5.3
IIb	4	6.4	31.9	5.3

(Table VI), but had no influence on placental weight (Table VIII). Since anti-oxytocin administration to pregnant rats did not change pup weight (Kumaresan *et al.*, 1971), maternal oxytocin, which is able to cross the placenta (Chard, 1972), cannot be important for intrauterine growth.

An increased fetal body weight (Table VI) as well as placental weight (Table VIII) was found after administration of α -MSH to brain-aspirated fetuses. Much more work needs to be done on the intermediate lobe hormone after this surprising finding, especially since MSH has been determined at an early stage in the pituitary glands of human fetuses (Kastin *et al.*, 1968).

Hypothalamic extracts

Four Sephadex G-25 fractions (A, B, C and E) of the entire base of the brain of 3-4-month-old calves were kindly supplied by Dr. A. Witter (Utrecht). These fractions have been prepared according to De Wied *et al.* (1969), except for the HCl extraction, which was performed ultrasonically at 0°C for 5 min, and the separation on Sephadex which was performed at 4°C. Solutions of the 4 fractions in physiological saline were neutralized to pH 7 by means of 0.5 N NaOH.

In preliminary experiments, 10 or 100 μ g of fraction C in physiological saline and 100 or 500 μ g of fraction C in oleum rapae did not change either body or placental weight in brain-aspirated fetuses. In intact fetuses, 5 mg of fractions B, C and E per fetus did not increase body or placental weight. Also 5 mg of fraction C per fetus at pH 5, 6 or 8 did not induce body weight or placental weight changes (Tables VI-IX).

Since 5 mg of fraction A per fetus caused death of the pregnant rats, this extract has been administered in a lower dose (50 μ g). This dose did not cause a significant in-

crease in fetal body weight (Table VII). It did, however, increase placental weight in the experiments reported in Table IX. However, in later experiments, this effect of fraction A did not appear to be reproducible.

Insulin

Although no specific hypothalamic factor seems to control the endocrine pancreas, insulin secretion is influenced by various neuroendocrine and neural mechanisms (Ensink and Williams, 1972; Malaisse, 1972). The excessive fetal growth during gestational diabetes mellitus is supposed to be causally related to a fetal hyperinsulinism (Hoet, 1969; Jost and Picon, 1970). To obtain this increased fetal growth, a normal hypothalamo-hypophyseal system should be necessary (De Gasparo and Hoet, 1971; Van Assche *et al.*, 1970), although an observation of Frandsen and Stakemann (1964) is conflicting in this respect. Since the endocrine pancreas in anencephalics is found to be less developed (Van Assche, 1968), the hypothalamo-hypophyseal system may thus be necessary for complete morphological and functional maturation of the pancreatic endocrine tissue (Van Assche *et al.*, 1970). Moreover, rat fetal plasma insulin increases 5-fold (Freie and Bouman, 1973) in the same period as we observed an increased fetal growth rate in intact fetuses (Swaab and Honnebier, 1973). These data, pointing to a functional connection between hypothalamus and pancreas made it of interest in the framework of the present study to investigate the influence of insulin upon fetal and placental development.

Insulin has been found in fetal pancreas (Jack and Milner, 1972; Fujimoto and Williams, 1972; Freie and Bouman, 1973) and in blood (Freie and Bouman, 1973; Grumbach and Kaplan, 1973). The placental block to insulin transfer (Jost and Picon, 1970) between the mother and the fetus is probably only partial (Solomon and Friesen, 1968; Knobil and Josimovich, 1959; Spellacy, 1971; Gitlin *et al.*, 1965).

Insulin tardum (Organon), injected in a dose of 2 I.U. into 3 litters of brain-aspirated rat fetuses on day 19, caused maternal death in 2 cases. From the one living animal the 5 live fetuses (of the total litter of 11) did not show increased growth, and nor did the placenta. Lower doses were not able to increase either fetal weight (Tables VI, VII) or placental weight (Table VIII). Picon (1967) obtained an increased fetal weight by means of insulin administration to intact fetuses, but he treated only half the litter. The question arises therefore whether this scheme of insulin, administered to the whole litter, would also cause death of the mother, and could thus be considered to be an unphysiological dose. Since decapitation of rabbit fetuses increases fetal plasma insulin level, and glucose induces increased insulin release from the pancreas of these animals (Jack and Milner, 1973), while the body weight of decapitated rabbit fetuses does not change (Jost, 1966a), the role of insulin in intrauterine growth of rabbit does not seem to be important.

In the adult situation a complex relationship exists between insulin and growth hormone. In adult rats (Salter and Best, 1953) and human ateleotic dwarfs (Editorial, 1953) insulin shows a growth promoting effect and a nitrogen retention effect respectively. In addition, growth hormone was reported to stimulate insulin secretion (Martin

TABLE VI
INFLUENCE ON FETAL BODY WEIGHT

Tables VI-IX. Influence of various substances on rat fetal body weight and placental weight. The general animal treatment, operation procedure and brain-aspiration were performed according to Swaab and Honnebie (1973). All animals were operated ("brain-aspiration") or sham operated ("intact") on the morning of day 19 of pregnancy. The animals received their hormones in a volume of 50 μ l (cf. Heggestad and Wells, 1965; Nourmura, 1959) of sterile physiological saline (0.9% NaCl) subcutaneously into the back by means of a 0.50 mm $\times$ 16 mm needle, unless mentioned otherwise in the tables. Doses were given per fetus, and the whole litter was treated in the same way. The controls received 50 μ l of 0.9% NaCl only, using the same procedure. In order to correct the fetal weights for differences in cranial filling, all fetal weights reported in these tables were measured after emptying the cranial cavity by suction (Swaab and Honnebie, 1973). The differences between the groups were tested by Student *t*-test (De Jonge, 1963, chapt. 13) and $P < 0.05$ was considered to be statistically significant.

Treatment of brain-aspirated fetuses	n mothers	n fetuses	Experimental group body weight (and S.E.M.)	n mothers	n fetuses	Control group body weight (and S.E.M.)	Student <i>t</i> -test	Result
<i>Rat growth hormone</i> ; NIAMD-RAT	6	45	2.65 (0.063)	5	51	2.87 (0.053)	$P < 0.02$	$\downarrow$
GH-B-1; 150 μ g								
ACTH: Cortrosyn (Organon); 150 μ g	5	37	3.11 (0.095)	5	51	3.09 (0.070)	$0.80 < P < 0.90$	—
ACTH: Cortrosyn-Depot (Organon); 50 μ l depot containing 1 mg/ml	5	47	3.09 (0.058)	5	56	3.44 (0.042)	$P < 0.001$	$\downarrow$
TSH; NIH-TSH-S6 (ovine); 150 μ g	5	39	2.95 (0.067)	5	43	2.97 (0.090)	$0.60 < P < 0.70$	—
Prolactin; NIH-P-S9 (ovine); 150 μ g	5	52	3.07 (0.056)	5	41	3.20 (0.097)	$0.20 < P < 0.30$	—
LH; NIH-LH-S18 (ovine); 150 μ g	4	39	3.23 (0.072)	5	26	3.23 (0.100)	$P > 0.9995$	—
FSH; NIH-FSH-S9 (ovine); 150 μ g	5	42	3.13 (0.069)	5	29	3.18 (0.098)	$0.80 > P > 0.70$	—
HCG; Pregnyl (Organon); 10 I.U.	4	37	3.23 (0.044)	5	51	3.17 (0.048)	$0.30 < P < 0.40$	—
Piton-S; (Organon, 10 U/ml) 0.5 U	5	40	3.22 (0.050)	5	48	3.41 (0.042)	$P < 0.01$	$\downarrow$
Hypothalamic extract	5	38	2.69 (0.083)	5	48	3.41 (0.042)	$P < 0.001$	$\downarrow$
Fraction-C, 5 mg								
Insulinum Tardum; 0.4 I.U. (Organon) 40 I.U./ml diluted 1/5 with phys. sal.	5	32	3.18 (0.067)	5	39	3.28 (0.053)	$0.20 < P < 0.30$	—
Insulinum Tardum; 0.2 I.U. (Organon) 40 I.U./ml diluted 1/10 with phys. sal.	5	44	2.90 (0.069)	5	39	3.28 (0.053)	$P < 0.001$	$\downarrow$
Placenta Suspensata-depot (Schwarzhaupt); 50 μ l	5	45	3.54 (0.055)	5	48	3.65 (0.038)	$0.10 < P < 0.20$	—
Cyclic AMP; N ⁶ -2'-O-Dibutyryl-adenosine-3': 5'-monophosphate, cyclic, monosodium salt (Boehringer), 150 μ g	5	40	3.57 (0.062)	5	41	3.58 (0.060)	$0.90 < P < 0.95$	—
α -MSH; 150 μ g	9	84	3.38 (0.043)	8	75	2.92 (0.039)	$p < 0.001$	$\uparrow$

TABLE VII

INFLUENCE ON FETAL BODY WEIGHT

Treatment of intact fetuses	n mothers	n fetuses	Experimental group body weight (and S.E.M.)	n mothers	n fetuses	Control group body weight (and S.E.M.)	Student t-test	Result
Rat growth hormone (see Table VI); 150 µg	5	41	4.02 (0.082)	5	50	4.13 (0.055)	0.10 < P < 0.20	—
Hypothalamic extract	5	45	3.98 (0.065)	5	56	3.84 (0.059)	0.20 > P > 0.10	—
Fraction A; 50 µg	5	35	3.67 (0.072)	5	44	3.69 (0.059)	0.90 > P > 0.80	—
Hypothalamic extract	5	50	3.66 (0.066)	5	51	3.93 (0.037)	P < 0.001	↓
Fraction B; 5 mg	8	67	3.71 (0.048)	8	81	3.87 (0.041)	0.01 < P < 0.02	↓
Hypothalamic extract	5	41	3.71 (0.106)	5	50	3.84 (0.069)	0.40 > P > 0.30	—
Fraction C; 5 mg	6	57	3.65 (0.056)	5	51	3.81 (0.054)	0.05 < P < 0.10	—
Hypothalamic extract	8	76	3.69 (0.053)	8	81	3.81 (0.034)	0.05 < P < 0.10	—
Fraction E; 5 mg								
Insulinum Tardum (see Table VI); 0.2 I.U./fetus								
Cyclic AMP (see Table VI); 150 µg								

TABLE VIII
INFLUENCE ON PLACENTAL WEIGHT

Treatment of brain-aspirated fetuses	n mothers	n fetuses	Experimental group, placental weight (and S.E.M.)	n mothers	n fetuses	Control group placental weight (and S.E.M.)	Student t-test	Result
<i>ACTH</i> : Cortrosyn (Organon); 150 µg	5	37	0.51 (0.021)	5	51	0.48 (0.008)	0.10 < <i>P</i> < 0.20	—
<i>ACTH</i> : Cortrosyn-Depot (Organon); 50 µl depot containing 1 mg/ml	5	47	0.50 (0.013)	5	56	0.50 (0.013)	0.95 < <i>P</i> < 0.975	—
<i>TSH</i> : NIH-TSH-S6; 150 µg	5	39	0.48 (0.012)	5	43	0.49 (0.012)	0.60 < <i>P</i> < 0.70	—
<i>Prolactin</i> NIH-P-S9; 150 µg	5	52	0.50 (0.009)	5	41	0.49 (0.011)	0.60 < <i>P</i> < 0.70	—
<i>LH</i> : NIH-LH-S18 (ovine); 150 µg	4	39	0.54 (0.013)	5	26	0.53 (0.022)	0.70 > <i>P</i> > 0.60	—
<i>FSH</i> : NIH-FSH-S9 (ovine); 150 µg	5	42	0.53 (0.011)	5	29	0.52 (0.021)	0.70 > <i>P</i> > 0.60	—
<i>HCG</i> : Pregnyl (Organon); 10 I.U.	4	37	0.50 (0.010)	5	51	0.49 (0.010)	0.95 < <i>P</i> < 0.975	—
<i>Piton-S</i> (Organon 10 U/ml); 0.5 U	5	40	0.50 (0.010)	5	48	0.51 (0.010)	0.60 < <i>P</i> < 0.70	—
<i>Hypothalamic extract</i> Fraction C; 5 mg	5	38	0.48 (0.012)	5	48	0.51 (0.010)	0.10 < <i>P</i> < 0.20	—
<i>Insulinum Tardum</i> (see before); 0.4 I.U.	5	32	0.48 (0.010)	5	39	0.49 (0.009)	0.50 < <i>P</i> < 0.60	—
<i>Insulinum Tardum</i> (see before); 0.2 I.U.	5	44	0.50 (0.010)	5	39	0.49 (0.009)	0.30 < <i>P</i> < 0.40	—
<i>Placenta Suspensata-depot</i> (Schwarzhaupt); 50 µl	5	45	0.49 (0.011)	5	48	0.54 (0.012)	<i>P</i> < 0.01	↓
<i>Rat growth hormone</i> (see Table VI); 150 µg	6	45	0.54 (0.014)	5	51	0.49 (0.011)	<i>P</i> < 0.02	↑
<i>α-MSH</i> ; 150 µg	9	84	0.51 (0.007)	8	75	0.45 (0.006)	<i>P</i> < 0.001	↑
<i>Cyclic AMP</i> (see Table VI); 150 µg	5	40	0.57 (0.013)	5	41	0.51 (0.009)	<i>P</i> < 0.001	↑

TABLE IX
INFLUENCE ON PLACENTAL WEIGHT

Treatment of intact fetuses	n mothers	n fetuses	Experimental group placental weight (and S.E.M.)	n mothers	n fetuses	Control group placental weight (and S.E.M.)	Student t-test	Result
Hypothalamic extract Fraction B; 5 mg	5	35	0.53 (0.012)	5	44	0.55 (0.014)	0.30 > P > 0.20	—
Hypothalamic extract Fraction C; 500 µg	5	50	0.52 (0.012)	5	51	0.51 (0.007)	0.40 < P < 0.50	—
Hypothalamic extract Fraction C; 5 mg	8	67	0.54 (0.012)	8	81	0.53 (0.007)	0.60 < P < 0.70	—
Hypothalamic extract Fraction E; 5 mg	5	50	0.54 (0.012)	5	41	0.52 (0.008)	0.50 > P > 0.40	—
Insulinum Tardum (see Table VI); 0.2 I.U.	5	57	0.50 (0.010)	5	51	0.51 (0.009)	0.30 < P < 0.40	—
Cyclic AMP (see Table VI); 150 µg	8	76	0.51 (0.011)	8	81	0.52 (0.006)	0.50 < P < 0.60	—
Rat growth hormone (see Table VI); 150 µg	5	41	0.55 (0.012)	5	50	0.51 (0.009)	P < 0.02	↑
Hypothalamic extract Fraction A; 50 µg	5	45	0.57 (0.010)	5	56	0.52 (0.009)	P < 0.005	↑

and Gagliardino, 1967), and was found to be unable to cause anabolism of protein in the absence of insulin (Editorial, 1953). Hypophysectomized rats had a lower insulin content and production of the pancreas, while the normal reaction to glucose administration was not found. This reaction was restored by growth hormone (Hoet, 1969). Whether or not a functional relationship between insulin and growth hormone also exists in the fetus has still to be studied.

At present, therefore, there are not sufficient data to justify calling insulin "the fetal growth hormone", as has been done in the literature (Hoet, 1969).

THE ROLE OF THE FETAL PITUITARY IN PARTURITION

The idea that the fetal pituitary could play a role in the initiation of parturition has arisen from observations of congenital malformations. Predisposition for prolonged pregnancy was reported in anencephaly without hydramnios (Malpas, 1933). In addition, a prolonged gestation occurred in Guernsey cattle having an inherited adeno-hypophyseal aplasia (Kennedy *et al.*, 1957) and in cyclopic sheep fetuses. The latter anomaly, caused by the ingestion of *Veratrum californicum*, is accompanied by absence or displacement of the fetal pituitary (Binns *et al.*, 1964). From the already classical experiments performed mainly in sheep and involving adrenalectomy, fetal hypophysectomy and administration of ACTH or adrenal glucocorticoids, the role of the fetal hypothalamo-hypophyseal-adrenal system in the initiation of labor has obtained experimental support (Drost and Holm, 1968; Liggins *et al.*, 1967; Liggins and Kennedy, 1968; Liggins, 1969). Additional evidence is that about the time of delivery, fetal plasma cortisol (Bassett and Thorburn, 1969; Nathanielsz *et al.*, 1972) and plasma ACTH (Alexander *et al.*, 1971, 1973) increase. In Ango goats habitual abortion was found to be accompanied by adrenal hyperplasia (Osinga, 1969). In addition, the finding of remarkably high posterior lobe hormone and neurophysin levels in fetal blood, apparently produced by the fetus (Chard *et al.*, 1970, 1971; Chard, 1971; Hoppenstein *et al.*, 1968; Robinson *et al.*, 1971), pointed to a possible involvement of the fetal hypothalamo-neurohypophyseal system in parturition.

However, observations in other animals and in man make the role of the fetal hypophysis questionable, at least as a general mechanism in the animal kingdom. Fetal adrenalectomy in rats gave varying results being partly against the "Liggins" hypothesis mentioned above. Josimovich (1969, and personal communication) found that after adrenalectomy on day $19\frac{1}{4}$ and $19\frac{3}{4}$ of pregnancy, an increasing proportion of pregnancies lasted a good day beyond term (nothing is known however, about the dispersion in gestation length of the fetuses born earlier!), while the same operation carried out between day $18\frac{1}{2}$ and $19\frac{1}{8}$ did not produce a significant amount of increased gestation lengths. Kirsch (1938) could not demonstrate that the rat fetuses would be essential for the determination of gestation length. In rats bearing brainless fetuses, gestation length did not appear to be prolonged (Swaab and Honnebier, 1973). Moreover, in contradistinction to the sheep (see above), fetal adrenal activity seems to decrease before birth in rat (Jost, 1966b, 1973; Cohen, 1963). In addition,

after injection (on day 19) of ACTH (Cortrosyn[®], Cortrosyn-depot[®]) in brain-aspirated fetuses (see Table VI) parturition never occurred within the next 48 h, although the fetal adrenals were clearly activated (Table V).

In a preliminary experiment on rabbits we observed that after fetal brain aspiration on day 25 (day of copulation is day 1 of pregnancy) the experimental animal as well as the sham operated control delivered on the expected time (day 32), while in the experimental animal two well-formed and well-aspirated fetuses were recovered and one macerated fetus. The mother probably ate the other 10 fetuses (Nathanielsz and Swaab, unpublished observation, Cambridge 1973). This is in agreement with the normal gestation length of decapitated rabbit fetuses in reduced litters (Jost, 1973). These observations certainly need confirmation since they are in disagreement with the "Liggins" hypothesis that has obtained additional experimental support in this species by the finding that cortisone can initiate parturition (Kendall and Liggins, 1972).

Donovan and Peddie (1973) showed that damage of the hypothalamus of the guinea-pig even causes abortion instead of the expected prolonged gestation. Increased fetal adrenal activity was not the sole course of parturition in this species (Donovan and Peddie, 1974).

Fetal hypophysectomy in the monkey, performed by placement of radioactive sources in the sella turcica, was associated with prolongation of gestation (Chez *et al.*, 1970). However, Mueller-Heubach *et al.* (1972) observed that after fetal adrenalectomy, labor was initiated at or near term in the majority of instances. Another argument against the "Liggins" hypothesis in this species is the finding of Van Wagenen and Catchpole (1965) that after removal of the fetus the placenta was born at normal term. This phenomenon has also been reported for rat (Kirsch, 1938) and mouse (Newton, 1935).

The few observations of Hutchinson *et al.* (1962) in pregnant monkeys suggested that delivery at normal term was possible after fetal hypophysectomy.

Human anencephalics do not have a normal functional hypothalamus (see above). In spite of the general opinion in the literature (*e.g.* Malpas, 1933; Jost, 1966a; Liggins and Kennedy, 1968; Milic and Adamsons, 1969) the supposed prolonged gestation length in anencephaly without hydramnios was not confirmed by our observations. The mean gestation length (36.6 weeks) in this anomaly was even much shorter than that of the control group (39.6 weeks). Spontaneously born anencephalics from pregnancies where there was a normal amount of amniotic fluid had a similar mean gestation length (39.7 weeks) as had the control group (39.6 weeks) although a high percentage of both pre- and post-maturely born anencephalics was observed (Honnebier and Swaab, 1973a). In spite of the abrupt rise in fetal cortisol observed in spontaneously born children, again suggesting a role of the adrenal in the initiation of parturition (Murphy, 1973), congenital adrenal hyperplasia is reported not to influence gestation length (Price *et al.*, 1971). These arguments show that the relationship between adrenal weight and pregnancy length, as proposed by Anderson *et al.* (1971), does not exist in human. Four children reported in the literature have a congenital aplasia of the hypophysis, and do not show a prolonged gestation length

(Table III). In addition, initiation of parturition could not be obtained by transabdominal injections of corticotropins, HCG or posterior lobe hormones (Honnebier and Swaab, 1973b; Honnebier *et al.*, 1974).

Therefore, strong evidence for a role of the fetal pituitary in the initiation of parturition only exists in sheep. However, since fetal hypophysectomy in this species has necessarily to be executed rather a long time (6 days) before term (Liggins, 1969), the influence of growth inhibition (*cf.* Liggins and Kennedy, 1968) certainly needs to be investigated before drawing a firm conclusion even here.

CONCLUSIONS

Elimination of the fetal brain or fetal hypophyseal area causes a reduction of fetal ponderal growth in various animal species. The same phenomenon is found in the human anencephalus. In addition, absence of fetal brain in rat and human is accompanied by a decreased placental growth. The primary cause of the ponderal growth inhibition will probably be situated in the hypothalamo-hypophyseal system.

The influence of hypophyseal hormones, hypothalamic extracts and related compounds on the development of the feto-placental unit were therefore tested by injection of these compounds directly into intact or brain-aspirated fetuses. Results of a pilot study are reported in the present study. Several compounds of hypophyseal origin were found to increase placental weight (*i.e.*, growth hormone and α -MSH), while α -MSH also increases fetal body weight. More work is needed to see how these actions are interrelated and what their physiological function might be.

Although observations on congenital anomalies and experiments on sheep suggested an essential role for the fetal hypothalamo-hypophyseal system in the initiation of labor, several observations plead against such a role in other species at present. Particularly in rat and human, the moment of initiation of parturition was found to be independent of the fetal hypothalamus. Since the delivery phase of brain-aspirated fetuses was considerably protracted (Swaab *et al.*, 1973), the fetal brain may rather play a role in the *course* of labor than in its *initiation*.

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REFERENCES

- ALEXANDER, D. P., BRITTON, H. G., FORSLING, M. L., NIXON, D. A. AND RATCLIFFE, J. G. (1971) The concentration of adrenocorticotrophin, vasopressin and oxytocin in the foetal and maternal plasma of the sheep in the latter half of gestation. *J. Endocr.*, **49**, 179–180.
- ALEXANDER, D. P., BRITTON, H. G., FORSLING, M. L., NIXON, D. A. AND RATCLIFFE, J. G. (1973) Adrenocorticotrophin and vasopressin in foetal sheep and the response to stress. In *The Endocrinology of Pregnancy and Parturition. Experimental Studies in the Sheep, Proc. Int. Symp.*, C. G. PIERREPONT (Ed.), Alpha Omega Alpha Publishing, Cardiff, pp. 112–125.
- ANDERSON, A. B. M., LAURENCE, K. M., DAVIES, K., CAMPBELL, H. AND TURNBULL, A. C. (1971) Fetal adrenal weight and the cause of premature delivery in human pregnancy. *J. Obstet. Gynaec. Brit. Cwlth*, **78**, 481–488.
- ANGERVALL, L. AND LUNDIN, P. M. (1963) Hypophysectomy in pregnant rats with special reference to the endocrine organs of the offspring. *Acta endocr. (Kbh.)*, **42**, 591–600.
- ANGERVALL, L. AND MARTINSSON, A. (1969) Overweight in offspring of cortisone-treated pregnant rats. *Acta endocr. (Kbh.)*, **60**, 36–46.
- BASSETT, J. M. AND THORBURN, G. D. (1969) Foetal plasma corticosteroids and the initiation of parturition in sheep. *J. Endocr.*, **44**, 285–286.
- BASSETT, J. M., THORBURN, G. D. AND WALLACE, A. L. C. (1970) The plasma growth hormone concentration of the foetal lamb. *J. Endocr.*, **48**, 251–263.
- BATTAGLIA, F. C. (1970) Intrauterine growth retardation. *Amer. J. Obstet. Gynec.*, **106**, 1103–1114.
- BINNS, W., JAMES, L. F. AND SHUPE, J. L. (1964) Toxicosis of *Veratrum californicum* in ewes and its relationship to a congenital deformity in lambs. *Ann. N.Y. Acad. Sci.*, **111**, 571–576.
- BLINKOV, S. M. AND GLEZER, I. I. (1968) *The Human Brain in Figures and Tables. A Quantitative Handbook*, Basic Books, Plenum Press, New York, p. 336, Table 115.
- BLIZZARD, R. M. AND ALBERTS, M. (1956) Hypopituitarism, hypoadrenalism, and hypogonadism in the newborn infant. *J. Pediatr.*, **48**, 782–792.
- BOER, K., BOER, G. J. AND SWAAB, D. F. (1974) Does the hypothalamo-neurohypophysial system play a role in gestation length or parturition? In *Integrative Hypothalamic Activity, Progress in Brain Research, Vol. 41*, D. F. SWAAB AND J. P. SCHADÉ (Eds.), Elsevier, Amsterdam, pp. 307–320.
- BREWER, D. B. (1957) Congenital absence of the pituitary gland and its consequences. *J. Path. Bact.*, **73**, 59–67.
- BUTTERSTEIN, G. M. AND LEATHEM, J. H. (1970) Ribosomes in normal and giant placentae. *J. Endocr.*, **48**, 473–474.
- C.B.S. (Centraal Bureau voor de Statistiek) (1972) Maandstatistiek van bevolking en volksgezondheid, Jaarg. 20, Suppl. In *Jaaroverzicht Bevolking en Volksgezondheid 1971*, Staatsuitgeverij, 's-Gravenhage, p. 62.
- CHARD, T. (1971) Recent trends in the physiology of the posterior pituitary. In *Current Topics in Experimental Endocrinology, Vol. 1*, L. MARTINI AND V. H. T. JAMES (Eds.), Academic Press, New York, pp. 81–120.
- CHARD, T. (1972) The posterior pituitary in human and animal parturition. *J. Reprod. Fertil., Suppl.* **16**, 121–138.
- CHARD, T., BOYD, N. R. H., FORSLING, M. L., MCNEILLY, A. S. AND LANDON, J. (1970) The development of a radioimmunoassay for oxytocin: the extraction of oxytocin from plasma, and its measurement during parturition in human and goat blood. *J. Endocr.*, **48**, 223–234.
- CHARD, T., HUDSON, C. N., EDWARDS, C. R. W. AND BOYD, N. R. H. (1971) Release of oxytocin and vasopressin by the human foetus during labour. *Nature (Lond.)*, **234**, 352–354.
- CHEZ, R. A., HUTCHINSON, D. L., SALAZAR, H. AND MINTZ, D. H. (1970) Some effects of fetal and maternal hypophysectomy in pregnancy. *Amer. J. Obstet. Gynec.*, **108**, 643–650.
- COHEN, A. (1963) Corrélation entre l'hypophyse et le cortex surrénal chez le fœtus de rat. Le cortex surrénal du nouveau-né. *Arch. Anat. micr. Morph. exp.*, **52**, 279–289.
- CONKLIN, P. M., SCHINDLER, W. J. AND HULL, S. F. (1973) Hypothalamic thyrotropin releasing factor. *Neuroendocrinology*, **11**, 197–211.
- CRAMER, D. W., BECK, P. AND MAKOWSKI, E. L. (1971) Correlation of gestational age with maternal human chorionic somatomammotropin and maternal and fetal growth hormone plasma concentrations during labor. *Amer. J. Obstet. Gynec.*, **109**, 649–655.
- CROSKERRY, P. G., SMITH, G. K., SHEPARD, B. J. AND FREEMAN, K. B. (1973) Perinatal brain DNA in the normal and growth hormone-treated rat. *Brain Res.*, **52**, 413–418.

- D'ANGELO, S. A. AND WALL, N. R. (1972) Maternal-fetal endocrine interrelations: effects of synthetic thyrotrophin releasing hormone (TRH) on the fetal pituitary-thyroid system of the rat, *Neuroendocrinology*, **9**, 197-206.
- DAWES, G. S. (1968) The placenta and foetal growth. In *Foetal and Neonatal Physiology*, G. S. DAWES (Ed.), Yearbook Medical Publishers, Chicago, Ill., pp. 42-59.
- DE GASPARO, M. AND HOET, J. J. (1971) Normal and abnormal foetal weight gain. In *Excerpta Medica International Congress Series No. 231, Proc. VII Congr. Intern. Diabetes Federation, Buenos Aires, 23-28 August, 1970*, K. R. RODRIGUEZ AND J. VALLANCE-OWEN (Eds.), pp. 667-677.
- DE JONGE, H. (1963) *Inleiding tot de Medische Statistiek, Vol. I and II*, Nederlands Instituut voor Preventieve Geneeskunde, Leiden.
- DELOST, P. (1971) Fetal endocrinology and the effect of hormones on development. In *The Biopsychology of Development*, E. TOBACH, L. R. ARONSON AND E. SHAW (Eds.), Academic Press, New York, pp. 195-229.
- DE WIED, D., WITTER, A., VERSTEEG, D. H. G. AND MULDER, A. H. (1969) Release of ACTH by substances of central nervous system origin. *Endocrinology*, **85**, 561-569.
- DICKER, S. E. AND TYLER, C. (1953) Vasopressor and oxytocic activities of the pituitary glands of rats, guinea pigs and cats and of human foetuses. *J. Physiol. (Lond.)*, **121**, 206-214.
- DONOVAN, B. T. AND PEDDIE, M. J. (1973) Foetal hypothalamic and pituitary lesions, the adrenal glands and abortion in the guinea pig. In *Foetal and Neonatal Physiology*, K. S. COMLINE *et al.* (Eds.), Cambridge Univ. Press, Mass., pp. 603-605.
- DONOVAN, B. T. AND PEDDIE, M. J. (1974) The adrenal glands, oestrogen, and the control of parturition in the guinea pig. In *Integrative Hypothalamic Activity, Progress in Brain Research, Vol. 41*, D. F. SWAAB AND J. P. SCHADÉ (Eds.), Elsevier, Amsterdam, pp. 281-288.
- DROST, M. AND HOLM, L. W. (1968) Prolonged gestation in ewes after foetal adrenalectomy. *J. Endocr.*, **40**, 293-296.
- DUNN, J. M. (1966) Anterior pituitary and adrenal absence in a live-born normocephalic infant, *Amer. J. Obstet. Gynec.*, **96**, 893-894.
- DUPOUY, J.-P. ET JOST, A. (1970) Activité corticotrope de l'hypophyse foetale du rat: influence de l'hypothalamus et des corticostéroïdes. *C. R. Soc. Biol. (Paris)*, **164**, 2422-2427.
- EDITORIAL (1953) Insulin and growth. *Brit. med. J.*, **II**, 383-384.
- EDWARDS, C. R. W. (1971) Measurement of plasma and urinary vasopressin by immunoassay. *Proc. roy. Soc. Med.*, **64**, 842-844.
- EGUCHI, Y. (1961) Atrophy of the fetal mouse adrenal following decapitation in utero, *Endocrinology*, **68**, 716-719.
- EGUCHI, Y. (1969) Interrelationships between the fetal and maternal hypophyseal-adrenal axes in rats and mice. In *Physiology and Pathology of Adaptation Mechanisms: Neural-Neuroendocrine-Humoral*, E. BAJUSZ (Ed.), Pergamon Press, Oxford, pp. 3-27.
- ENGFELDT, B. AND HULTQUIST, G. T. (1953) Administration of crystalline growth hormone to pregnant rats. *Acta endocr. (Kbh.)*, **14**, 181-188.
- ENSINCK, J. W. AND WILLIAMS, R. H. (1972) Hormonal and nonhormonal factors modifying man's response to insulin. In *Handbook of Physiology, Vol. I, Endocrinology*, R. O. GREEP, E. B. ASTWOOD, D. F. STEINER, N. FREINKEL AND S. R. GEIGER (Eds.), American Physiological Society, Williams and Wilkins, Baltimore, Md., pp. 665-684.
- ERENBERG, A. AND FISHER, D. A. (1973) Thyroid hormone metabolism in the foetus. In *Foetal and Neonatal Physiology, Proc. Sir Joseph Barcroft Centenary Symposium*, K. S. COMLINE *et al.* (Eds.), Cambridge Univ. Press, Mass., pp. 508-526.
- FOSTER, D. L., KARSCH, F. J. AND NALBANDOV, A. V. (1972) Regulation of luteinizing hormone (LH) in the fetal and neonatal lamb. II. Study of placental transfer of LH in the sheep. *Endocrinology*, **90**, 589-592.
- FRANCHIMONT, P. (1971) *Sécrétion Normale et Pathologique de la Somatotrophine et des Gonadotrophines Humaines*, Masson, Paris, p. 306.
- FRANDSEN, V. A. AND STAKEMANN, G. (1964) The site of production of oestrogenic hormones in human pregnancy. III. Further observations on the hormone excretion in pregnancy with anencephalic foetus. *Acta endocr. (Kbh.)*, **47**, 265-276.
- FREIE, H. M. P. EN BOUMAN, P. R. (1973) Perinatale spiegels van insuline en glucose bij de rat. *14e Federatieve Vergadering van medisch-biologische Verenigingen, Groningen, 26-28 april, 1973*, Abstract No. 125.

- FUJIMOTO, W. Y. AND WILLIAMS, R. H. (1972) Insulin release from cultured fetal human pancreas. *Endocrinology*, **91**, 1133–1136.
- FUJITA, T., EGUCHI, Y., MORIKAWA, Y. AND HASHIMOTO, Y. (1970) Hypothalamic-hypophyseal adrenal and thyroid systems: observations in fetal rats subjected to hypothalamic destruction, brain compression and hypervitaminosis A. *Anat. Rec.*, **166**, 659–672.
- FURTH, E. D. AND PAGLIARA, A. S. (1971) Thyroid hormones. In *Endocrinology of Pregnancy*, F. FUCHS AND A. KLOPPER (Eds.), Harper and Row, London, pp. 216–234.
- GAMMAL, E. B. (1973) Effects of placental lesions on foetal growth in rats. *Experientia (Basel)*, **29**, 201–203.
- GITLIN, D., KUMATE, J. AND MORALES, C. (1965) On the transport of insulin across the human placenta. *Pediatrics*, **35**, 65–69.
- GRUENWALD, P. (1963) Chronic fetal distress and placental insufficiency. *Biol. Neonat. (Basel)*, **5**, 215–265.
- GRUENWALD, P. (1966) Growth of the human fetus. II. Abnormal growth in twins and infants of mothers with diabetes, hypertension, or isoimmunization. *Amer. J. Obstet. Gynec.*, **94**, 1120–1132.
- GRUMBACH, M. M. AND KAPLAN, S. L. (1973) Ontogenesis of growth hormone, insulin, prolactin and gonadotropin secretion in the human foetus. In *Foetal and Neonatal Physiology, Proc. Sir Joseph Barcroft Centenary Symposium*, K. S. COMLINE *et al.* (Eds.), Cambridge Univ. Press, Mass., pp. 462–487.
- HEGGETAD, C. B. AND WELLS, L. J. (1965) Experiments on the contribution of somatotrophin to prenatal growth in the rat. *Acta anat. (Basel)*, **60**, 348–361.
- HOET, J. J. (1969) Normal and abnormal foetal weight gain. In *Ciba Foundation Symposium on Foetal Autonomy*, G. E. W. WOLSTENHOLME AND M. O'CONNOR (Eds.), Churchill, London, pp. 186–217.
- HONNEBIER, W. J. AND SWAAB, D. F. (1973a) The influence of anencephaly upon intrauterine growth of fetus and placenta and upon gestation length. *J. Obstet. Gynaec. Brit. Cwlth*, **80**, 577–588.
- HONNEBIER, W. J. AND SWAAB, D. F. (1973b) The role of the human foetal brain in the onset of labour. *J. Endocrinol.*, **57**, xxx–xxxii.
- HONNEBIER, W. J., JÖBSIS, A. C. AND SWAAB, D. F. (1974) The effect of hypophyseal compounds and Human Chorionic Gonadotrophin (HCG) upon the anencephalic fetal adrenal and parturition in the human. *J. Obstet. Gynaec. Brit. Cwlth*, in press.
- HOPKINS, P. S. AND THORBURN, G. D. (1972) The effects of foetal thyroidectomy on the development of the ovine foetus. *J. Endocr.*, **54**, 55–66.
- HOPPENSTEIN, J. M., MILTENBERGER, F. W. AND MORAN, W. H. (1968) The increase in blood levels of vasopressin in infants during birth and surgical procedures. *Surg. Gynec. Obstet.*, **127**, 966–974.
- HULTQUIST, G. T. AND ENGFELDT, B. (1949) Giant growth of rat fetuses produced experimentally by means of administration of hormones to the mother during pregnancy. *Acta endocr. (Kbh.)*, **3**, 365–376.
- HUTCHINSON, D. L., WESTOVER, J. L. AND WILL, D. W. (1962) The destruction of the maternal and fetal pituitary glands in subhuman primates. *Amer. J. Obstet. Gynec.*, **83**, 857–865.
- HWANG, U. K. AND WELLS, L. J. (1959) Hypophysis–thyroid system in the fetal rat: thyroid after hypophyseopriva, thyroxin, triiodothyronine, thyrotrophin and growth hormone. *Anat. Rec.*, **134**, 125–141.
- INGLETON, P. M., ENSOR, M. AND HANCOCK, M. P. (1971) Identification of prolactin in foetal rat pituitary. *J. Endocr.*, **51**, 799–800.
- JACK, P. M. B. AND MILNER, R. D. G. (1972) Effect of foetal decapitation on the development of insulin secretion in the rabbit. *J. Endocr.*, **55**, xxvi.
- JACK, P. M. B. AND MILNER, R. D. G. (1973) Effect of decapitation on the development of insulin secretion in the foetal rabbit. *J. Endocr.*, **57**, 23–31.
- JEAN, CH. ET DELOST, P. (1969) Prolactine et embryogenèse mammaire chez la souris. *J. Physiol. (Paris)*, **61**, 323–324.
- JOHNSON, J. D., HANSEN, R. C., ALBRITTON, W. L., WERTHEMANN, U. AND CHRISTIANSEN, R. O. (1973) Hypoplasia of the anterior pituitary and neonatal hypoglycemia. *J. Pediatr.*, **82**, 634–641.
- JOSIMOVICH, J. B. (1969) The foetal role in the initiation of parturition in the ewe. In *Foetal Autonomy*, G. E. W. WOLSTENHOLME AND M. O'CONNOR (Eds.), Churchill, London, pp. 231–232 (discussion).
- JOST, A. (1954) Hormonal factors in the development of the fetus. *Cold Spr. Harb. Symp. quant. Biol.*, **19**, 167–181.
- JOST, A. (1966a) Anterior pituitary function in foetal life. In *The Pituitary Gland*, G. W. HARRIS AND B. T. DONOVAN (Eds.), Butterworths, London, pp. 299–323.

- JOST, A. (1966b) Problems of fetal endocrinology: the adrenal glands. In *Recent Progress in Hormone Research*, Vol. 22, G. PINCUS (Ed.), Academic Press, New York, pp. 541–574.
- JOST, A. (1971) Hormones in development: past and prospects. In *Hormones in Development*, M. HAMBURG AND E. J. W. BARRINGTON (Eds.), Appleton-Century-Crofts, New York, pp. 1–18.
- JOST, A. (1973) Does the foetal hypophyseal–adrenal system participate in delivery in rats and in rabbits? In *Foetal and Neonatal Physiology, Proc. Sir Joseph Barcroft Centenary Symposium*, K. S. COMLINE *et al.* (Eds.), Cambridge Univ. Press, Mass., pp. 589–593.
- JOST, A., DUPOUY, J. P. AND GELOSO-MEYER, A. (1970) Hypothalamo–hypophyseal relationships in the fetus. In *The Hypothalamus*, L. MARTINI, M. MOTTA AND FRASCHINI (Eds.), Academic Press, New York, pp. 605–615.
- JOST, A., DUPOUY, J. P. AND RIEUTORT, M. (1974) The ontogenetic development of hypothalamo–hypophyseal relations. In *Integrative Hypothalamic Activity, Progress in Brain Research*, Vol. 41, D. F. SWAAB AND J. P. SCHADÉ (Eds.), Elsevier, Amsterdam, pp. 209–219.
- JOST, A. AND PICON, L. (1970) Hormonal control of fetal development and metabolism. In *Advances in Metabolic Disorders*, Vol. 4, R. LEVINE AND R. LUFT (Eds.), Academic Press, New York, pp. 123–184.
- KAJIHARA, A., KOJIMA, A., ONAYA, T., TAKEMURA, Y. AND YAMADA, T. (1972) Placental transport of thyrotropin releasing factor in the rat. *Endocrinology*, **90**, 592–594.
- KAPLAN, S. L., GRUMBACH, M. M. AND SHEPARD, T. H. (1972) The ontogenesis of human fetal hormones I. Growth hormone and insulin. *J. clin. Invest.*, **51**, 3080–3093.
- KASTIN, A. J., GENNSEN, G., ARIMURA, A., CLINTON MILLER, III, M. AND SCHALLY, A. V. (1968) Melanocyte-stimulating and corticotrophic activities in human foetal pituitary glands. *Acta endocr. (Kbh.)*, **58**, 6–10.
- KENDALL, J. Z. AND LIGGINS, G. C. (1972) The effect of dexamethasone on pregnancy in the rabbit. *J. Reprod. Fertil.*, **29**, 409–413.
- KENNEDY, P., KENDRICK, J. W. AND STORMONT, C. (1957) Adenohypophyseal aplasia, an inherited defect associated with abnormal gestation in Guernsey cattle. *Cornell Vet.*, **47**, 160–178.
- KIRSCH, R. E. (1938) A study on the control of length of gestation in the rat with notes on maintenance and termination of gestation. *Amer. J. Physiol.*, **122**, 86–93.
- KITCHELL, R. L. AND WELLS, L. J. (1952) Functioning of the hypophysis and adrenals in fetal rats: effects of hypophysectomy, adrenalectomy, castration, injected ACTH and implanted sex hormones. *Anat. Rec.*, **112**, 561–585.
- KLOOSTERMAN, G. J. (1966) Prevention of prematurity, *Ned. T. Verlosk.*, **66**, 361–379.
- KLOOSTERMAN, G. J. (1970) On intrauterine growth. *Int. J. Gynaec. Obstet.*, **8**, 895–912.
- KLOOSTERMAN, G. J. AND HUIDEKOPER, B. L. (1954) The significance of the placenta in “Obstetrical mortality”. *Gynaecologia (Basel)*, **138**, 529–550.
- KNOBIL, E. AND CATON, W. L. (1953) The effect of hypophysectomy on fetal and placental growth in the rat. *Endocrinology*, **53**, 198–201.
- KNOBIL, E. AND JOSIMOVICH, J. B. (1959) Placental transfer of thyrotropic hormone, thyroxine, triiodothyronine, and insulin in the rat. *Ann. N.Y. Acad. Sci.*, **75**, 895–904.
- KUČERA, J. AND DOLEŽALOVÁ, V. (1972) Prenatal development of malformed fetuses at 28–42 weeks of gestational age. *Biol. Neonat. (Basel)*, **20**, 253–261.
- KUMARESAN, P., KAGAN, A. AND GLICK, S. M. (1971) Oxytocin antibody and lactation and parturition in rats. *Nature (Lond.)*, **230**, 468–469.
- LANMAN, J. T. AND SCHAEFFER, A. (1968) Gestational effects of fetal decapitation in sheep. *Fertil. and Steril.*, **19**, 598–605.
- LASCELLES, A. K. AND SETCHELL, B. P. (1959) Hypothyroidism in sheep. *Aust. J. biol. Sci.*, **12**, 455–465.
- LEVINA, S. E. (1972) Times of appearance of LH and FSH activities in human fetal circulation. *Gen. comp. Endocr.*, **19**, 242–246.
- LIGGINS, G. C. (1968) Premature parturition after infusion of corticotrophin or cortisol into foetal lambs. *J. Endocr.*, **42**, 323–329.
- LIGGINS, G. C. (1969) Premature delivery of foetal lambs infused with glucocorticoids. *J. Endocr.*, **45**, 515–523.
- LIGGINS, G. C. AND KENNEDY, P. C. (1968) Effects of electrocoagulation of the foetal lamb hypophysis on growth and development. *J. Endocr.*, **40**, 371–381.
- LIGGINS, G. C., KENNEDY, P. C. AND HOLM, L. W. (1967) Failure of initiation of parturition after electrocoagulation of the pituitary of the fetal lamb. *Amer. J. Obstet. Gynec.*, **98**, 1080–1086.

- LINCOLN, D. W. (1971) Labour in the rabbit: Effect of electrical stimulation applied to the infundibulum and median eminence. *J. Endocr.*, **50**, 607–618.
- LINCOLN, D. W. (1974) Maternal hypothalamic control of labor. In *Integrative Hypothalamic Activity, Progress in Brain Research, Vol. 41*, D. F. SWAAB AND J. P. SCHADÉ (Eds.), Elsevier, Amsterdam, 1974, pp. 289–306.
- MALAISSÉ, W. J. (1972) Hormonal and environmental modification of islet activity. In *Handbook of Physiology, Sect. 7, Vol. 1, Endocrinology*, R. O. GREEP, E. B. ASTWOOD, D. F. STEINER, N. FREINKEL AND S. R. GEIGER (Eds.), Amer. Physiol. Soc., Williams and Wilkins, Baltimore, Md., pp. 237–260.
- MALPAS, P. (1933) Postmaturity and malformations of the foetus. *J. Obstet. Gynaec. Brit. Emp.*, **40**, 1046–1053.
- MARTIN, J. M. AND GAGLIARDINO, J. J. (1967) Effect of growth hormone on the isolated pancreatic islets of rat in vitro. *Nature (Lond.)*, **213**, 630–631.
- McKUSICK, V. A. AND RIMOIN, D. L. (1967) General Tom thumb and other midgets, *Sci. Amer.*, **217**, 102–110.
- MILIC, A. B. AND ADAMSONS, K. (1969) The relationship between anencephaly and prolonged pregnancy. *J. Obstet. Gynaec. Brit. Cwlth*, **76**, 102–111.
- MUELLER-HEUBACH, E., MYERS, R. E. AND ADAMSONS, K. (1972) Effects of adrenalectomy on pregnancy length in the rhesus monkey. *Amer. J. Obstet. Gynec.*, **112**, 221–226.
- MURPHY, B. E. P. (1973) Does the human fetal adrenal play a role in parturition? *Amer. J. Obstet. Gynec.*, **115**, 521–525.
- NATHANIELSZ, P. W., COMLINE, R. S., SILVER, M. AND PAISEY, R. B. (1972) Cortisol metabolism in the fetal and neonatal sheep. *J. Reprod. Fert.*, Suppl. **16**, 39–59.
- NEWTON, W. H. (1935) "Pseudo-parturition" in the mouse, and the relation of the placenta to postpartum oestrus. *J. Physiol. (Lond.)*, **84**, 196–207.
- NOUMURA, T. (1959) Development of the hypophyseal–adrenocortical system in the rat embryo in relation to the maternal system. *Jap. J. Zool.*, **10**, 279–300.
- O'DONOHUE, N. V. AND HOLLAND, P. D. J. (1968) Familial congenital adrenal hypoplasia. *Arch. Dis. Childh.*, **43**, 717–723.
- OSINGA, A. (1969) De "foeto-placentale unit" en het geboorteproces. *T. Diergeneesk.*, **94**, 768–776.
- PAGE, E. W. (1969) Human fetal nutrition and growth. *Amer. J. Obstet. Gynec.*, **104**, 378–387.
- PAINE, B. G. (1971) Growth and development. In *Endemic Cretinism, Proc. Symp. 1971, Inst. of Human Biology (Monograph Ser. No. 2)*, B. S. HETZEL AND P. O. PHAROAH (Eds.), Surrey Beatty, Chipping Norton, N.S.W., pp. 94–100.
- PREKH, M. C., BENJAMIN, F. AND GASTILLO, N. (1973) The influence of maternal human growth hormone secretion on the weight of the newborn infant. *Amer. J. Obstet. Gynec.*, **115**, 197–201.
- PICON, L. (1967) Effect of insulin on growth and biochemical composition of the rat fetus. *Endocrinology*, **81**, 1419–1521.
- PRICE, H. V., CONE, B. A. AND KEOGH, M. (1971) Length of gestation in congenital adrenal hyperplasia. *J. Obstet. Gynaec. Brit. Cwlth*, **78**, 430–434.
- RAYNAUD, A. (1950) Recherches expérimentales sur le développement de l'appareil génital et le fonctionnement des glandes endocrines des foetus de souris et de mulot, *Arch. Anat. micr. Morph. exp.*, **39**, 518–576.
- REID, J. D. (1960) Congenital absence of the pituitary gland. *J. Pediatr.*, **56**, 658–664.
- RIMOIN, D. L., MERIMEE, T. J. AND McKUSICK, V. A. (1966a) Growth hormone deficiency in man: an isolated recessively inherited defect. *Science*, **152**, 1635–1637.
- RIMOIN, D. L., MERIMEE, T. J. AND McKUSICK, V. A. (1966b) Sexual ateliotic dwarfism: A recessively inherited isolated deficiency of growth hormone. *Trans. Ass. Amer. Phycs*, **79**, 297–311.
- ROBINSON, A. G., ZIMMERMAN, E. A. AND FRANTZ, A. G. (1971) Physiologic investigation of posterior pituitary binding proteins neurophysin I and neurophysin II. *Metabolism*, **20**, 1148–1155.
- ROFFI, J. (1958) Dosage de la vasopressine dans l'hypophyse du foetus de rat en fin de gestation. *C. R. Soc. Biol. (Paris)*, **152**, 741–743.
- SALTER, J. AND BEST, C. H. (1953) Insulin as a growth hormone. *Brit. med. J.*, **II**, 353–356.
- SCHUTT, W. (1965) Foetal factors in intrauterine growth retardation. In *Clinics in Developmental Medicine*, M. DAWKINS AND B. MACGREGOR (Eds.), The Spastics Society Medical Education and Information Unit in ass. with Heinemann, London, No. **19**, pp. 1–9.
- SLOB, A. K. (1972) *Perinatal Endocrine and Nutritional Factors Controlling Physical and Behavioural Development in the Rat*, Med. Thesis, Offset Printing Bureau V.C.V.O., Vlaardingen.

- SOLOMON, S. AND FRIESEN, H. G. (1968) Endocrine relations between mother and fetus. *Ann. Rev. Med.*, **19**, 399-430.
- SPELLACY, W. N. (1971) Insulin. In *Endocrinology of Pregnancy*, F. FUCHS AND A. KLOPPER (Eds.), Harper and Row, New York, pp. 197-215.
- SWAAB, D. F. (1972) The hypothalamo-neurohypophysial system and reproduction. In *Topics in Neuroendocrinology, Progress in Brain Research, Vol. 38*, J. ARIËNS KAPPERS AND J. P. SCHADÉ (Eds.), Elsevier, Amsterdam, pp. 225-244.
- SWAAB, D. F. AND HONNEBIER, W. J. (1973) The influence of removal of the fetal rat brain upon intrauterine growth of the fetus and the placenta and on gestation length. *J. Obstet. Gynaec. Brit. Cwlth*, **80**, 589-597.
- SWAAB, D. F., HONNEBIER, W. J. AND BOER, K. (1973) The role of the foetal rat brain in labour. *J. Endocr.*, **57**, xxxi-xxxii.
- THOMSON, A. M., BILLEWICZ, W. Z. AND HYTTEN, F. E. (1968) The assessment of fetal growth. *J. Obstet. Gynaec. Brit. Cwlth*, **75**, 903-916.
- TUCHMANN-DUPLESSIS, H. ET GABE, M. (1960) Absence de produit de neurosécrétion dans la post-hypophyse des anencephales. *Bull. Acad. Méd. (Paris)*, **144**, 102-104.
- VAN ASSCHE, F. A. (1968) A morphological study of the Langerhans' islets of the fetal pancreas in late pregnancy. *Biol. Neonat. (Basel)*, **12**, 331-342.
- VAN ASSCHE, F. A., GEPTS, W. AND DE GASPARO, M. (1970) The endocrine pancreas in anencephalics. A histological, histochemical and biological study. *Biol. Neonat. (Basel)*, **41**, 374-388.
- VAN WAGENEN, G. AND CATCHPOLE, H. R. (1965) Growth of the fetus and placenta of the monkey. *Amer. J. Phys. Anthropol.*, **23**, 23-34.
- WINDLE, W. F., RHINES, R. AND RANKIN, J. (1943) A Nissl method using buffered solutions of thionin, *Stain Technol.*, **18**, 77-86.
- ZAMENHOF, S., MOSLEY, J. AND SCHULLER, E. (1966) Stimulation of the proliferation of cortical neurons by prenatal treatment with growth hormone. *Science*, **152**, 1396-1397.

DISCUSSION

JOST: I was very interested in your paper of course, especially in what you said about anencephalic infants having a normal mean gestation length. My limited observations on rabbits would, in agreement with your preliminary experiment, suggest that the fetal pituitary has no important effect upon the length of pregnancy or the initiation of delivery. The point you discussed about the role of the fetal hypothalamus in body growth seems also of importance. It is our experience that the encephalotomized young are consistently smaller than decapitated fetuses. My explanation was that the surgery we have to do for encephalotomizing the young is much more stressful to the uterus than for decapitation, which is a very simple operation. Were you suggesting that fetal growth hormone could control the size of the placenta, and thus the size of the fetus?

SWAAB: I did not mean to say that growth inhibition after brain aspiration is caused by the placenta that lacks growth hormone. Growth of the fetus and placenta are to a certain degree two separate entities. We can restore the placental weight after brain aspiration again by injecting growth hormone into the fetus, without increasing the fetal body weight.

LEQUIN: In the human it has been shown that the placental weight is correlated with HCS-levels. I just wonder why the placental lactogen was not mentioned here, since HCS-levels are very high.

SWAAB: We are of course mostly interested in hypophyseal and hypothalamic factors involving fetal growth. We tested, however, one preparation, placenta suspensata, that should contain HCS. It did not increase fetal body weight or placental weight. Perhaps we have to try a better HCS preparation.