Acta Paediatrica Academiae Scientiarum Hungaricae Vol. 9 (2), pp. 159—180 (1968)

Anencephaly and the Development of the Male Genital Tract

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(Received September 11, 1967)

Introduction

Anencephaly in male foetuses is a rare abnormality. All series of anencephalics studied show a high proportion of females, as judged by the appearance of the external genitalia. Female preponderance was reported by Potter [58] 9 to 1, Zander [78] 2 to 1, Ballantyne [2] 3 to 1, Covell [20] 5 to 1, Record and McKeown [67] 2 to 1, and Hilman [29] 4 to 1. In a personal series of 60 anencephalics, 13 were male. The possibility that this disturbed sex ratio could be explained on the grounds that some of the phenotypic female foetuses were genetic males showing complete sex reversal was investigated by studying their nuclear chromatin pattern [57, 55, 4, 5]. These studies demonstrated that in all cases the nuclear chromatin corlresponds to the phenotypic sex. No evidence of complete sex reversal was seen. In four male anencephalics the chromosomes were found to be normal [27, 26].

However, although these investigations indicate that complete sex reversal does not occur, there is evidence from the results of experimental endocrinology in the rabbit foetus for supposing that the genital tract of the human male foetus might show at least partial sex reversal. Jost [37] demonstrated that the removal of the pituitary from the rabbit foetus by foetal decapitation in utero, results in partial feminisation of the genital tract of the male foetuses and could be prevented by injecting gonadotrophic hormone into the foetus at the time of the decapitation. These experiments suggest that the foetal pituitary influences foetal testicular function and that in the absence of the foetal pituitary, testicular impairment results, with subsequent failure of the normal masculinisation of the genital tract.

Anencephalic foetuses have abnormalities of the endocrine glands, the best known being a small adrenal cortex [10]. The anterior pituitary was at one time thought to be absent, and Ballantyne [2] was unable to demonstrate this gland in most of his 45 cases; however, later investigators [20, 1] found it in all cases, although reduced in size.

In view of the results of experi-

mental endocrinology in the rabbit foetus, and the observations on the pituitary of human anencephalics, it is clearly possible that the male human anencephalic might show some degree of incomplete masculinisation of the genital tract as a result of foetal testicular insufficiency. To study this aspect of anencephaly, 13 male anencephalic foetuses have been investigated and observations on the development of the genital tract are now reported.

Material and Methods

A series of 13 stillborn male anencephalic foetuses and one normal male foetus were collected for this investigation. The crown-rump length was measured and a correction made to allow for the deformity of the head. The age of each foetus was estimated from the corrected crown-rump length using the data of Streeter [71].

The state of the development of the genital tract was studied in each specimen with particular regard to any abnormality in the appearance of the external genitalia. A general estimate was made of penis size and recorded as either normal or hypoplasic. The length of the dorsal surface of the penis was measured to the nearest mm. and was expressed as a percentage of crown-rump length and also of thigh length, measured from the pubic tubercle to the patella. The position of the urethral meatus was also recorded. The size of the scrotum was estimated and recorded as either normal, slightly hypoplasic or hypoplasic, and the presence of rugae on the scrotal skin was noted. The length and width of the scrotum was also measured. The scrotum length was expressed as a percentage of the crown-rump length and thigh length.

The position of the testes was determined in each foetus, and recorded as being either on the posterior abdominal wall, in the iliac fossa, in the inguinal canal or in the scrotum. The pelvis of each foetus was dissected for remains of the paramesonephric (Müllerian) ducts.

The head was X-rayed in each case for the presence or absence of a pituitary fossa.

A skin biopsy was taken from all foetuses, sectioned at 5μ, stained with haematoxylin and eosin, and the nuclei of 100 cells were examined for nuclear chromatin. Histological studies of the internal organs were not possible owing to post-mortem changes.

Results

Figures 1 to 7 show the external genitalia of 6 of the 13 anencephalics and one normal foetus. Table I summarises the observations on the state of development of the genital tract in the 13 anencephalic foetuses compared with the normal foetus.

In all 13 anencephalics, normal differentiation of the penis and scrotum had occurred, the urethral folds were normally fused and the urethral meatus was established at the tip of

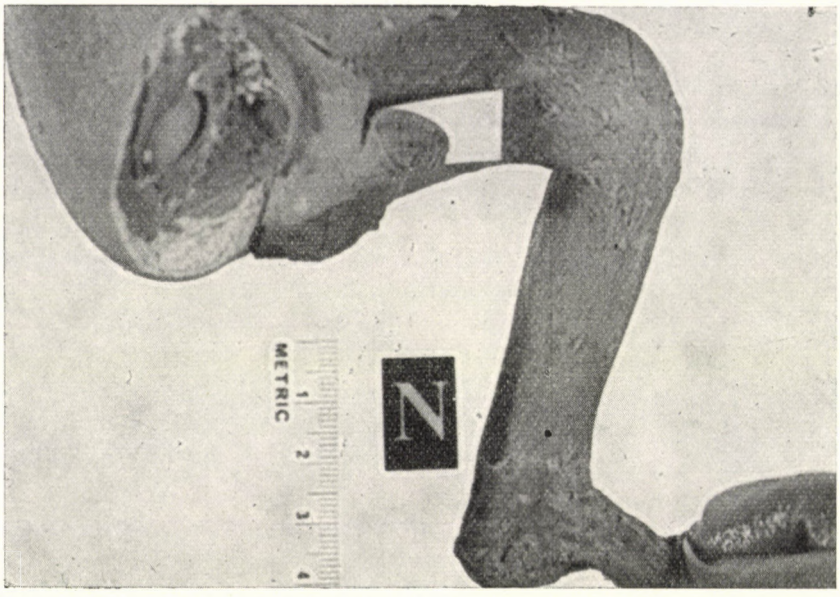

Fig. 1. Normal 30 week foetus showing normal penile development

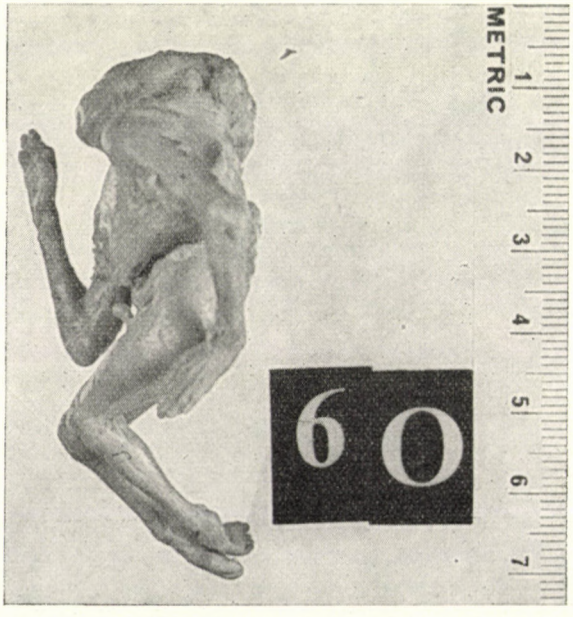

Fig. 2. Anencephalic foetus (No. 60) 10 weeks, with normally differentiated penis and scrotum

the penis except for foetus serial No. 10 which had a urethral opening on the undersurface of the glans but well beyond the corona. No evidence of partial feminisation and no evidence of hypospadias was seen.

Although normal differentiation of the male external genitalia was found in all cases, 9 of the 13 foetuses, serial Nos. 11, 10, 9, 38, 16, 56, 12, 35 and 55 showed well marked hypoplasia of the penis and scrotum. Four foetuses, serial Nos. 60, 26, 3 and 24, showed reasonably normal development of the external genitalia when compared with the normal foetus. However, 3 of the foetuses with hypoplasia of the penis, serial Nos. 16, 55 and 35, showed normal or near normal development of the scrotum.

Table II gives the measurements of the penis and scrotum in all the foetuses, and these measurements provide a good correlation with the observations recorded in Table I. The measurements have been recorded both as absolute figures and as a percentage of crown-rump and thigh length.

The testes had descended into the scrotum in 3 cases, serial Nos. 55, 24 and 3. These were foetuses with normal or near normal external genitalia. In 2 foetuses, serial Nos. 26 and 35, the testes were in the inguinal canal and in the remaining foetuses they were still within the abdominal cavity. No evidence of abnormal persistance of any part of the paramesonephric (Müllerian) ducts was found and no remnants of a uterus or tubes were seen.

The examination of the skin sections revealed that all foetuses were chromatin negative; in each foetus less than 5% of cells showed nuclear chromatin.

The X-ray of the skull of the normal foetus showed a well-formed pituitary fossa. The pituitary fossa was not present on X-ray in any of the 13 anencephalic foetuses.

These observations indicate that although the genital tract in the male anencephalic foetus undergoes completely normal differentiation with no evidence of partial feminisation, the subsequent growth in size of the external genitalia following the completion of differentiation may be markedly retarded. This retardation was particularly noticeable in 9 of the 13 anencephalic foetuses studied in this series.

Review of the Literature

Before these observations can be discussed it is necessary to review the present state of knowledge in several different but interrelated fields. (A) The chronology of the stages in the differentiation of the genital tract in normal male human foetuses. (B) The results of experimental endocrinology in the mammal foetus on the role of the foetal testis, pituitary and adrenal in male differentiation. (C) The ductless glands in anencephaly and related congenital abnormalities in the human foetus which also show interference with the hypothalamic-pituitary system.

TABLE I

The development of the genital tract of 13 male anencephalic foetuses and one normal foetus

Serial No.	Testis		Penis*		Scrotum*	
	Right	Left	Size	Position of meatal opening	Size	Rugae
Normal	Scrotum	Scrotum	Normal	At tip	+	Present
60	Posterior abdominal wall	Posterior abdominal wall	+	At tip	+	Absent
11	Right iliac fossa	Left iliac fossa	○	At tip	○	Absent
10	Posterior abdominal wall	Posterior abdominal wall	○	Under surface of glans	○	Absent
9	Right iliac fossa	Left iliac fossa	○	At tip	○	Absent
26	Inguinal canal	Inguinal canal	+	At tip	+	Absent
38	At deep inguinal ring	At deep inguinal ring	○	At tip	○	Absent
16	Posterior abdominal wall	Posterior abdominal wall	○	At tip	+	Absent
56	At deep inguinal ring	In inguinal canal	○	At tip	○	Absent
12	Right iliac fossa	Left iliac fossa	○	At tip	○	Absent
3	Scrotum	Scrotum	+	At tip	+	Present
35	Inguinal canal	Inguinal canal	○	At tip	±	Present
24	Scrotum	Scrotum	+	At tip	+	Present
55	Scrotum	Scrotum	○	At tip	+	Present

* Penis and scrotum size + Normal ± Slight hypoplasia ○ Hypoplastic

TABLE II

Measurements and weights of 13 male anencephalic foetuses and one normal foetus

Serial No	Age (wks)	Weight grams	Crown rump length mm	Thigh length mm	Crown rump length (corrected) mm	Penis length mm	Penis length		Scrotum		Scrotum length	
							% of C/R length	% of Thigh length	Length mm	Width mm	% of C/R length	% of Thigh length
Normal	30	1730	225	62.5	225	18	8.0	28.9	30	25	13.3	48.0
60	10	20.5	42	20	52	4.5	10.7	22.5	5.5	3.0	13.1	27.5
11	24	340	110	49	140	6	5,4	12.2	9	7	8.2	18.4
10	24	652	138	62	163	8	5.8	12.9	12	10	8.7	19.3
9	24	340	140	51	156	9	6.4	17.6	10	7	7.1	19.6
26	24	964	140	58	170	16	11.4	27.6	22	10	15.7	37.9
38	25	482	160	54	175	6	3.7	11.1	14	6	8.7	25.9
16	26	766	180	62	195	8	4.4	12.9	22	15	12.2	35.5
56	28	1098	185	77	220	7	3.8	9.1	14	7	7.6	18.2
12	29	1502	220	76	250	7	3.2	9.2	15	10	6.8	19.7
3	30	1474	228	81	255	17	7.4	20.9	25	19	10.9	30.9
35	32	1814	240	84	270	12	5.0	14.3	25	15	10.4	29.7
24	32	1503	240	86	280	21	8.7	24.4	29	22	12.1	33.7
55	34	1786	280	83	310	14	5.0	16.9	34	20	12.1	40.9

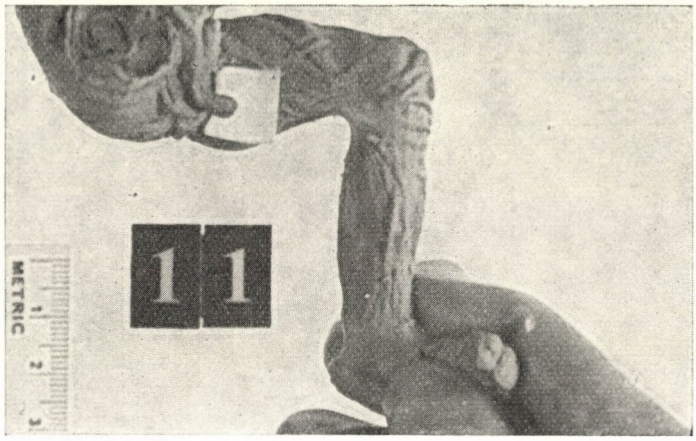

FIG. 3. Anencephalic foetus (No. 11) 24 weeks, with hypoplasic penis and scrotum

FIG. 4. Anencephalic foetus (No. 10) 24 weeks, with hypoplasic penis and scrotum

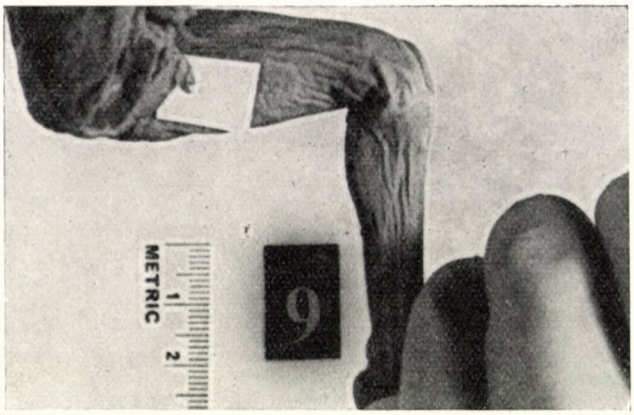

FIG. 5. Anencephalic foetus (No. 9) 24 weeks, with hypoplasic penis and scrotum

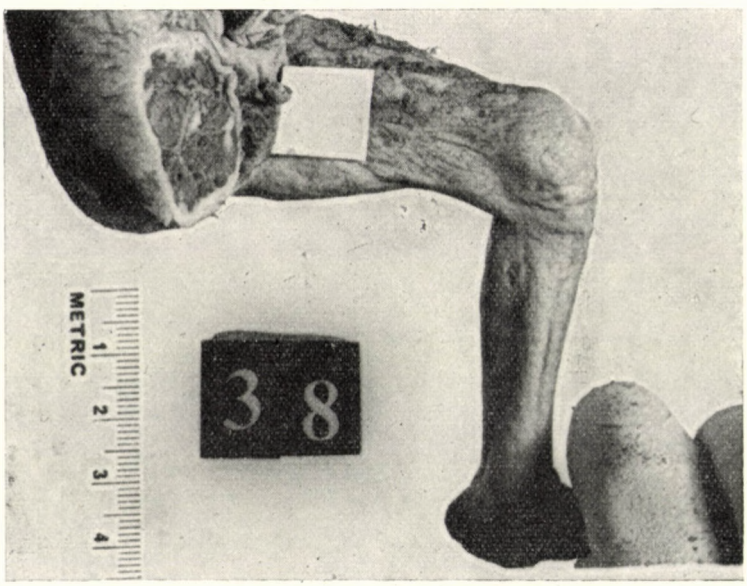

FIG. 6. Anencephalic foetus (No. 38) 25 weeks, with hypoplasic penis and scrotum

A) *Differentiation of the male genital tract in the human foetus*

In the human foetus the chronology of the stages in the differentiation of the male genital tract has been studied by several investigators and the results are now well established.

1. The foetal testis. The primitive gonad first becomes recognisable as a testis in embryos of 14—16 mm crown-rump length. At this time seminiferous tubules are found into which the germ cells become incorporated. At the 27 mm stage the gonad of the male embryo is now a

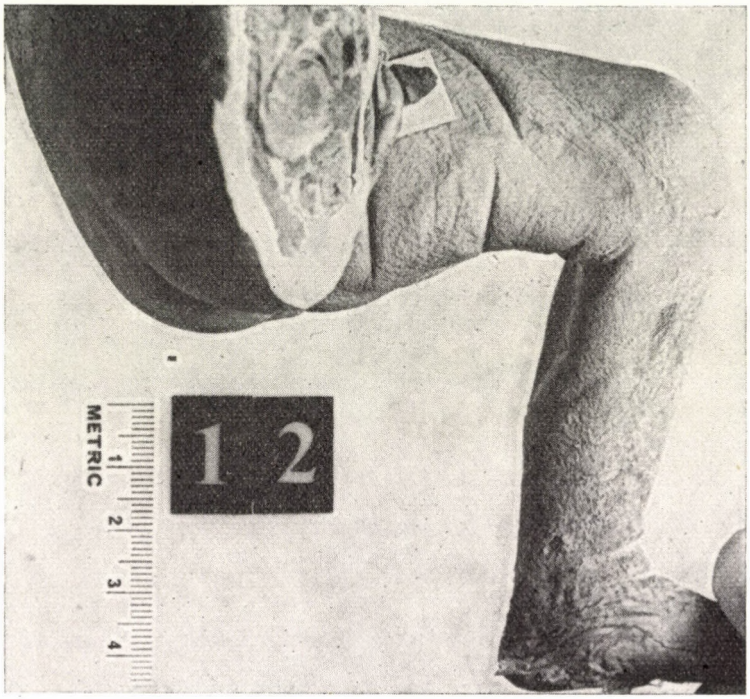

FIG. 7. Anencephalic foetus (No. 12) 29 weeks, with hypoplasic penis and scrotum

typical testis. The interstitial cells first show signs of specialisation in embryos of the 31 mm stage and by the 50 mm stage they increase rapidly in numbers to form large areas of hypertrophied cells between the seminiferous tubules. This increase continues up to the 160 mm stage after which a rapid decline in their number occurs [23].

2. *The internal ducts.* At the 27 mm stage, when the gonad is first recognisable as a testis, the genital tract has not as yet started to differentiate into a male. It is still to be regarded except for the testes as sexually undifferentiated and consists of the urogenital sinus into which open on each side the mesonephric (Wolffian) duct and the paramesonephric (Müllerian) duct. From 32 mm onwards the Müllerian ducts regress and the Wolffian ducts differentiate into the vasa deferentia, including the seminal vesicles. The first buds of the prostate appear at the 50 mm stage [38].

3. *The external genitalia.* The differentiation of the external genitalia of the male foetus starts later at the 50 mm stage [24]. In the undifferentiated state, the external genitalia consist of the genital tubercle, the urethral groove and urethral folds and the genital swellings. From 50 mm onwards the urethral folds fuse, bringing the urogenital ostium ultimately to the glans penis, to form the penile urethra, the line of fusion

being represented by the perineal raphe. The corpora cavernosa are formed by the 70 mm stage [32]. By the 100 mm stage the urinary meatus is established at the tip of the penis, and the external genitalia are fully differentiated by the 135 mm stage. From this time onwards the interstitial cells in the testis dwindle in number and size [24]. Descent of the testes into the scrotum does not occur until the 230 mm stage, 7 months, onwards [77].

The time during which active differentiation of the male genital tract is taking place, from the 32 mm to the 100 mm stage, i.e. up to the 4th month of intra-uterine life, coincides with the proliferation of the interstitial cells of the foetal testis. That these cells might be of importance in development was first suggested by BOUIN and ANCEL [14] who reported that the interstitial cells of the pig foetal testis were active and suggested that they might be responsible for male differentiation. From this idea has stemmed a long series of experimental observations in mammals concerning the role of the foetal gonads on sexual differentiation.

B) *Experimental endocrinology in mammal foetuses on male development*

1. The role of the foetal testis. LILLIE [43, 44, 45] noted the masculinisation of the genital tract in freemartins in cattle. The freemartin is the female of heterosexual twins of cattle which is partially masculinised. The assumption was then made that this masculinisation was due to the effect of hormones from the testes of the male twin, and LILLIE himself suggested the experiment of castration of the embryo. First attempts at foetal castration were made by MOORE [48, 49] in the opossum. The operation was performed after sexual differentiation had started and failed to stop further differentiation of the male genital tract. Similar experiments were performed by WELLS and FRALICK [75] in the rat. They castrated male rat foetuses when differentiation was nearly completed and found that subsequent development, as judged by the growth of the seminal vesicles and the bulbourethral glands, was retarded although otherwise normal differentiation occurred.

However, when the castration of the male foetus is performed before or at the beginning of differentiation of the male genital tract, the Wolffian ducts regress and the Müllerian ducts persist and develop into a uterus, as observed by JOST [35], in the rabbit and RAYNAUD and FRILLEY [64, 65], in the mouse. Similar results were obtained by in vitro experiments on explanted rat tissues [62].

If the castration is performed at an intermediate stage, when differentiation of the male genital tract has only just started, this results in partial male differentiation, with hypospadias of the external genitalia [37].

These experiments indicate that the foetal testis has the main responsibility in differentiating the sexes; in its absence the gonadless foetus de-

velops along feminine lines. The experiments indicate that the foetal testis is of essential importance in *initiating* male differentiation. It is for this reason that castration will only result in feminine development when performed before differentiation has started. If the castration of the male foetus is performed after differentiation has been initiated by the foetal testes, male development continues, although this may be incomplete or at a reduced rate, depending on how late the castration is carried out.

This evidence in the rabbit and mouse, indicating that the foetal testis is essential for intiating male differentiation, is now confirmed for man by cases of human phenotypic females with an XY sex chromosome complement [28, 19, 11]. These cases are referred to as "Pure Gonadal Dysgenesis" to distinguish them from Ovarian Dysgenesis or Turner's Syndrome. If an eponym were to be awarded to "Pure Gonadal Dysgenesis", it should be Jost's syndrome in view of his outstanding contribution to the understanding of the problem. In these human cases each testis is replaced by a gonadal streak and the syndrome is therefore equivalent to the male rabbit foetuses castrated by JOST at 19 days which subsequently developed as females.

2. The role of the foetal pituitary. The role of the foetal pituitary in regulating the functional development of the foetal testis is much less well established and the experimental results are somewhat conflicting.

In the rat, foetal hypophysectomy by decapitation early in sexual differentiation results in slight under-development of the male genital tract [39]. In mice hypophysectomised by X-rays prior to differentiation of the male genital tract, normal development occurs, the only difference being a reduction in the number of gonocytes in the foetal testis [66, 63].

If the decapitation is performed when male differentiation is nearly completed, no abnormality is found except for some reduction in the interstitial cells of the testis. These results may be interpreted in two ways; either the foetal testis of the rat and mouse functions independently of the foetal pituitary or an alternative source of gonadotrophin is available which controls the foetal testis.

Further experiments in the rat suggest that the foetal testis is under hormonal control from the foetal pituitary. When the foetal testis of the rat is grafted into the seminal vesicle of a castrated adult rat, stimulation occurs and interstitial cells develop in the foetal testis. These changes do not occur when the graft is performed in hypophysectomised and castrated hosts, unless gonadotrophins are injected [36, 39, 37]. It is therefore probable that in the decapitated rat or mouse foetus some alternative source of gonadotrophic hormone from the placenta compensates for the loss of the foetal pituitary.

The results in the rabbit are, however, strikingly different. When the foetus is hypophysectomised by de-

capitation just before differentiation starts, on day 19, abnormalities of the male genital tract occur. The Müllerian ducts regress and the Wolffian ducts differentiate normally into vasa deferentia and epididymes although slight under-development of the seminal vesicles is found. The prostate however is markedly underdeveloped and the external genitalia are feminine in appearance. If gonadotrophin is given at the time of the decapitation, normal development occurs. In a detailed analysis of the pituitary regulation of the rabbit foetal testis, JOST [37] provided evidence that the pituitary acts at a critical stage between day 22 and day 24 of development, and that this coincides with the presence of McManus positive material in the pituitary on day 22. These McManus positive granules decrease on day 23 to day 24, suggesting an out-pouring of hormone from the pituitary at this stage.

This evidence supports the view that in the rabbit, the foetal testis is regulated by the foetal pituitary at a critical stage in development and does not function independently. However, the evidence indicates that the pituitary regulation of the foetal testis in the rabbit is only partial, since complete feminisation of the foetus does not occur when hypophysectomy is performed at the beginning of male differentiation on day 19. Foetal castration at this stage results in complete sex reversal of the male foetus [37].

These experiments support the view that in male human anencephalics testicular function is normal up to the 100 mm stage, so resulting in completely normal differentiation of the male genital tract and the normal regression of the Müllerian ducts. However, after the 100 mm stage, some partial reduction in testicular function may occur, leading to the hypoplasia of the external genitalia which was present in 9 of the 13 anencephalics.

It is suggested that this partial testicular deficiency after the 100 mm stage is due directly to the deficiency of the hypothalamic-pituitary system which is present in these anencephalic foetuses, and to the subsequent loss of foetal pituitary gonadotrophic hormones.

3. The role of the foetal adrenals. Whether the foetal adrenals produce androgens in amounts sufficient to influence the differentiation of the Wolffian ducts is still an open question. The adrenal of the foetal guinea pig is capable of maintaining prostatic development in tissue culture as effectively as the testis and this effect applies equally to adrenals from male or female guinea pigs [60, 61]. Furthermore it is widely recognised that adrenal hyperplasia in the human foetus produces varying degrees of masculinisation of the female foetus [30, 11]. In the rat, MOORE [50] reported no stimulation of the seminal vesicles, JOST and GELOSO [40] found a slight stimulation near the adrenal graft, and PRICE and INGLE [59] reported stimulation of the seminal vesicles, prostate and coagulating glands of adult castrated rats by autotransplanting foetal adrenals.

KITCHELL and WELLS [42] found that foetal adrenalectomy in the rat had no effect on the growth of the seminal vesicles, the growth of the seminal vesicles was similar in castrated or adrenalectomised–castrated foetuses.

In the rabbit no direct experiments have yet been performed but since JOST [37] produced complete feminisation of the male foetus following castration, clearly the foetal adrenal can have no effect on the Wolffian ducts in this species. The balance of evidence at present would therefore support the view that the foetal adrenals do not normally play any significant role in the development of the male genital tract.

C) *Endocrine organs in anencephaly and related abnormalities*

1. Anencephaly. Although BALLANTYNE [2] was unable to find the pituitary in any of his series of 46 anencephalics and BROWNE [17] could not find the gland in his series of 5 anencephalics, later workers have been able to identify it in all the cases studied [3, 20, 1, 18].

ANGEVINE [1], found the pituitary in all of a series of 20 anencephalics and reported that the anterior pituitary was present in all cases and no conscpicuous differences were noted when compared with the anterior pituitary from normal foetuses. The pars intermedia was found in 6, and the pars nervosa in only 5 cases. The three parts of the gland were found in only 3 of the 20 anencephalics. He did not describe the gonads or the genital tract.

CH'IN [18] studied 15 cases. 7 were at full term, 4 were 8 month foetuses, and 4 were 7 month foetuses. The sella was malformed in all cases but in spite of this he was able to find the anterior pituitary in every case. No description was given of the genital tract or the external genitalia.

PERRIN and BENIRSCHKE [55] in a series of 35 anencephalics reported on the gonads of 27 and described them as being "unremarkable save for immaturity". They also stated that the "observed structure of the internal and external genitalia did not manifest any hermaphroditic abnormalities". No detail of the size of the external genitalia was given. POTTER [58] stated that the gonads and sex organs in anencephaly are normal.

BENIRSCHKE [10] described the adrenals in anencephaly and hydrocephaly and reviewed the literature. He found that the adrenals develop normally up to the twentieth week and from then on, the foetal zone, which constitutes 80—85% of the gland in the normal full term foetus, undergoes degeneration. Similar findings were reported in hydrocephaly provided the hypothalamus was affected. The marked atrophy of the adrenal is due to the premature involution of the foetal zone of the adrenal cortex, occurring from the twentieth week onward. BENIRSCHKE suggested, as have previous workers, that this adrenal atrophy is secondary to the interference with the hypo-

thalamic-pituitary system in these foetuses.

2. *Congenital absence of the pituitary.* There are occasional reports in the literature of foetuses with congenital absence of the pituitary with an otherwise normal skull and brain. The most recent report [70] gives details of a male child born without a pituitary who survived until 17 years of age. The child showed hypothyroidism, hypoadrenalism and hypogonadism and had a marked hypoplasia of the external genitalia. However, the photograph published shows that the penis and scrotum although very small are normally differentiated. The testes were in the inguinal canal and were unusually small and soft. Histologically only atrophic remnants of seminiferous tubules were present. REID [68] described a full term white boy who died soon after birth, weighing 8 pounds. The pituitary was absent and a small nodule, histologically containing no pituitary cells, was present on the base of the brain. The sella turcica was normal and covered with a complete diaphragma sellae. No anterior pituitary tissue was found on serial section through the base of the skull and the posterior pharynx. The genitourinary tract was normal but the testes were smaller than would be expected. The external genitalia were normally developed. This case indicates that both normal differentiation and growth of the male genital tract can occur in the complete absence of pituitary.

BLIZZARD and ALBERTS [12] described a full term white male born following an uneventful pregnancy, who died soon after birth. The external genitalia were notably small for a male newborn infant, although the urethral meatus opened normally at the end of the glans. At postmortem the pituitary was absent and the pituitary fossa although present was about half normal size. The adrenal glands were very small and devoid of a foetal cortex. The testes were undescended and lying on the pelvic wall, and were smaller than normal. Histologically they showed a complete absence of interstitial cells. The thymus was larger than normal but histologically appeared normal.

JACKSON and HOFFENBERG [34] described a case of hypopituitarism and gonadal dysgenesis. The patient was a male dwarf aged 70 with minute external genitalia. The photograph in their paper indicates that the penis and scrotum although very small, were normally differentiated. At postmortem the pituitary was found to be minute, 3 mm in diameter, and the testes were undescended and extremely small.

BREWER [15] reported two cases of congenital absence of the pituitary, one with a normal head and the other with cyclopia and a large encephalocele. The first was a female who died five hours after birth following a pregnancy of 34½ weeks. The adrenals were very small and histologically consisted of a poorly formed zona glomerulosa and a zone resembling the zona fasciculata. No further details were given. The thyroid was also small and the acini were

mostly small and empty. The ovaries and uterus were normal. The second case was a 28 week male still-born foetus. The adrenals were reported as being very much reduced in size. The testes were in the upper part of the inguinal canal and were normal. No details on the state of development of the external genitalia were given.

MOSIER [51] described female twins which died soon after birth. One twin died at 2 days and showed marked adrenal hypoplasia, but no observations were made on the pituitary. The second twin died after four days and was examined in more detail. The pituitary was very small and the adrenals were minute and microscopically the three layers were present in normal proportions; only traces of the foetal cortex were found. The ovaries were normal.

EHRLICH [22] reported the case of a 15 month girl who died following grand mal convulsions from the age of 12 months. At postmortem the sella turcica was present and roofed in with dura, but did not contain a pituitary. A small nodule was found anteriorly and inferiorly to the optic chiasma which proved to be a collection of anterior pituitary cells on section. Some ectopic anterior pituitary cells were also found in the roof of the pharynx. The adrenals, thyroid and ovaries were histologically normal.

3. Hydrocephaly. BENIRSCHKE's [10] series included 5 cases of hydrocephaly associated with gross damage to the hypothalamus, 3 of which were males. All had hypoplasia of the adrenals. In one, no testes were identified and in the other two the interstitial cells were reported as few or involuting. No details were given on the development of the external genitalia.

4. Cyclopia. The pituitary has very occasionally been reported as congenitally absent in human foetuses with an associated abnormality of the head such as cyclopia or encephalocele [78]. EDMONDS [21] described 5 cases of cyclopia in which the pituitary was absent in 3 and present in the remaining 2. In the 3 cases without a pituitary 2 were female and 1 was male. The gonads of the apituitary foetuses, both the ovary and the testis, showed no significant deviation from normal. No description of the genital tract was given. He also reported that the adrenals were markedly hypoplasic in the 3 foetuses without a pituitary, but normal in the 2 foetuses in which the pituitary was present. He found that in 63 cases in papers located through the Index-Catalogue, Fourth Series [33] the presence or absence of a pituitary was only specified 11 times and was reported as absent in 6 cases. OZAWA [52] reported smallness of the thyroid, adrenals and testes in a cyclopic foetus without a pituitary.

5. Hydranencephaly. WATSON [74] described a male child with hydranencephaly which died 7 days after birth in which the pituitary was absent. The adrenals were hypoplasic; the thyroid and thymus were reported as normal. No description was given of the genital tract.

It is clear from this review that little attention has been paid in the past to the state of development of the genital tract in anencephaly and related abnormalities. This is due to the very recent appreciation of the importance of the foetal testis and pituitary in the differentiation and growth of the genital tract in mammals. However, these reports tend to confirm the observations on male anencephalic foetuses made in this paper that the human abnormalities which show gross interference with the hypothalamic-pituitary system may have hypoplasia of a normally differentiated male genital tract.

Discussion

This investigation and the review of the literature raises three points for discussion. (A) The observation that normal differentiation of the male genital tract occurs in anencephaly and related conditions in spite of the gross interference with the hypothalamic-pituitary system. (B) The observation that marked hypoplasia of the male external genitalia may occur in many but not all of these foetuses. (C) The female preponderance which is reported in all series of anencephalic foetuses.

A) *Normal differentiation*

This investigation indicates that normal differentiation of the male genital tract occurs in anencephalic foetuses, and similar observations have been reported in foetuses with related abnormalities such as cyclopia with absence of the pituitary, hydrocephaly with destruction of the hypothalamus and congenital absence of the pituitary with an otherwise normal head as reviewed earlier in this paper. The common pathology in these abnormal foetuses is a gross interference with the hypothalamic-pituitary system and all show marked hypoplasia of the adrenals, a finding which is consistently associated with lesions of the hypothalamic-pituitary system.

It is of especial interest to note, that the smallest foetus in the series, serial No. 60, with a crown-rump length of only 54 mm already has fully differentiated external genitalia with the urethral meatus at the tip of the penis. Although Wilkins [76] on page 302 in a drawing of the external genitalia implies that the urethral folds are normally still unfused up to the fourth month, this is not in agreement with the embryological data reviewed earlier in this paper and confirmed in this early foetus. It is therefore concluded that the hypothalamic-pituitary system of the human foetus is not essential for the normal differentiation of the male genital tract which is completed by the 100 mm stage, at the fourth month. Since normal male differentiation has occurred in these foetuses it is also concluded that the functional activity of the foetal testis in anencephaly is normal up to the 100 mm stage in spite of the gross interference with the hypothalamic-pituitary system.

The explanation for this normal testicular function cannot be given with certainty. However, it is suggested that the normal testicular function in anencephalic foetuses up to the 100 mm stage is due to the high level of chorionic gonadotrophic hormone present up to the end of the fourth month. After this time the high level falls abruptly [72, 16]. The foetal testis during this critical period of differentiation of the genital tract would therefore be under a stimulation from the placental gonadotrophic hormone which may compensate for the deficiency of its own hypothalamic-pituitary system. This may also be the mechanism in the mouse and the rat and explain the normal differentiation which follows the decapitation of these male foetuses. However, in the rabbit since decapitation of the foetus does result in partial feminization of the genital tract, clearly chorionic gonadotrophin is unable to compensate for the loss of the foetal pituitary.

An alternative explanation that the early function of the foetal testis in man may be completely independent of hormonal control either from the foetal pituitary or the placenta cannot be ruled out entirely although the experimental evidence is against it. Experiments in the rat were carried out to test this idea [36, 39]. The foetal testis of the rat was grafted into the seminal vesicles of adult castrated rats with or without their hypophyses. In the hypophysectomised castrate the graft shows very few interstitial cells and exercises little or no action. However, in the castrated male with an intact pituitary the interstitial cells of the graft are hypertrophic and the evidence of secretory activity is considerable. Under these conditions the function of the foetal testis clearly depends on hypophyseal stimulation. Further experiments in the rabbit [37] reviewed earlier in this paper show that foetal decapitation results in partial feminisation of the male genital tract.

These experiments in both the rat and the rabbit strongly support the view that the function of the foetal testis is under hormonal control and that it does not function autonomously during differentiation of the genital tract.

It might further be argued that the foetal pituitary of anencephalic foetuses although hypoplasic and without hypothalamic connections, could function normally in the human anencephalic foetus up to the 100 mm stage, so determining the normal testicular function up to this stage. There is no evidence to support this suggestion and it is unlikely in view of the reports already reviewed that normal differentiation of the male genital tract occurs in foetuses with congenital absence of the pituitary in a normal head. These cases indicate that normal early testicular function leading to normal differentiation can take place in spite of the complete absence of the foetal pituitary.

It is suggested that the foetal testis in man prior to the 100 mm stage may function normally under the in-

fluence of the placental gonadotrophic hormones and not come under the control of the foetal hypothalamic-pituitary system until later in development after differentiation of the genital tract is completed and the early high level of chorionic gonadotrophic hormone declines. The exact stage at which the pituitary is functionally active in the human foetus is uncertain although there is histochemical evidence for secretory activity in the human before the sixteenth week [53].

B) *Hypoplasia of the external genitalia in anencephaly*

The hypoplasia of the normally differentiated external genitalia indicates that foetal testicular function is reduced after the 100 mm stage. This observation is in agreement with the foetal castration experiments reviewed earlier which show that late castration results in a retardation in growth, although differentiation of the genital tract proceeds normally. It is suggested that this testicular insufficiency after the fourth month is due to the gross disturbance of the hypothalamic-pituitary system and the subsequent absence of foetal pituitary gonadotrophic hormone. The chorionic gonadotrophic hormone which is postulated as being responsible for stimulating the foetal testis prior to the 100 mm stage falls dramatically to a lower level after the fourth month, and the foetal testis is not stimulated to function adequately from then on.

The hypoplasia of the external genitalia in anencephaly may therefore be regarded as evidence that the foetal pituitary normally is responsible for stimulating the foetal testis after the fourth month and that the chorionic gonadotrophic hormone, because of its dramatic fall after the fourth month, is no longer able to compensate for the absence of foetal pituitary hormone. However, not all the male anencephalic foetuses show the marked hypoplasia of the external genitalia and some display external genitalia which are normal in size. It is not possible to explain this apparent discrepancy, but it is suggested that it may be due to the wide variation in the levels of chorionic gonadotrophic hormone present during the later months of pregnancy. Brody and Carlström [16] showed that the serum gonadotrophic hormone level varies from 30 iu per ml of serum down to less than 6 iu in women with male foetuses. It is thus possible that the anencephalic foetuses without hypoplasia of the external genitalia are from mothers with high levels of gonadotrophic hormone which provides the necessary stimulus for the foetal testis.

Adrenal hypoplasia is a constant finding in anencephaly and other abnormalities with damage to the hypothalamic-pituitary system and clearly placental hormones are unable to compensate for the loss of foetal pituitary adrenotrophic hormones.

The role, if any, of the foetal adrenal in the normal differentiation and growth of the male genital tract

of the human foetus is unknown. GROLLMANN [25] first suggested that the foetal zone of the foetal adrenal is androgenic and VINES [73] reported that the foetal zone of female foetuses exhibits a shorter androgenic phase than does that of males, based on fuchsin stains of the foetal adrenals. The foetal zone constitutes 80—85% of the gland [10] and, as reviewed earlier, is always atrophied in cases of anencephaly and related conditions in wich the hypothalamic-pituitary system is abnormal. However, studies of early anencephalic foetuses before the fifth month demonstrate that the development of the adrenal and its foetal zone proceeds normally up to 20 weeks [47, 41, 31, 10], and it is not until after the 20th week that the foetal zone undergoes involution. Since normal differentiation of the male genital tract is established by the end of the fourth month, it could be argued that androgens from the adrenals might compensate for the hypothalamic-pituitary deficiency in anencephaly and be responsible for the normal differentiation. This hypothesis is most unlikely in view of the report that male and female foetal adrenals contain approximately similar amounts of androgenic steroids in the same gestational periods [13]. and that these steroids probably take their origin from the foetal zone of the adrenal cortex. Furthermore in cases of congenital adrenal hyperplasia in females the Müllerian ducts are not inhibited in spite of the masculinisation of the external genitalia [11]. If the foetal testis were not functional in anencephaly, remains of the Müllerian ducts would be expected since inhibition of the Müllerian duct system is a function of the foetal testis [37] in addition to its effect on the Wolffian ducts and the external genitalia. JOST [37] demonstrated that androgens implanted into castrated rabbit foetuses did not suppress the Müllerian ducts, although causing normal development of the Wolffian ducts.

The possibility that the foetal adrenal hypoplasia which occurs after the fifth month determines the hypoplasia of the external genitalia in anencephaly rather then the fall in chorionic gonadotrophic hormone is also unlikely, in view of the observation that the androgen production is similar in female and male foetal adrenals [13]. If foetal adrenal androgens were adequate to maintain male development in the later part of pregnancy, some masculinisation of female foetuses would be expected to occur.

Human anencephalic foetuses have occasionally been reported as having a large thymus [58], and this enlargement has also been reported in foetuses with congenital absence of the pituitary [12]. The explanation for this enlargement has been determined experimentally in the rat and the rabbit by BEARN [6, 7, 8, 9], who has shown that foetal hypophysectomy by decapitation results in hyperplasia of the thymus with associated hypoplasia of the adrenals, and that these effects are abolished by injecting ACTH into the foetus at the time of

the decapitation. This experimental work indicates that the thymus hyperplasia in human anencephalics is secondary to the adrenal hypoplasia which follows the lesion of the hypothalamic-pituitary system.

C) *Female preponderance*

The disturbed sex ratio in anencephalic foetuses, 13 males in a series of 60 anencephalics, cannot be explained on the grounds that some of the genetic males have undergone sex reversal, since the nuclear chromatin of anencephalic foetuses always corresponds to the phenotypic sex [57, 55, 4]. In addition the chromosomes of anencephalic foetuses have been examined and reported as normal [27, 26]. The grounds for supposing that this sex reversal might occur in anencephaly springs from the experiments in the rabbit where decapitation to remove the foetal pituitary at the beginning of differentiation results in partial feminisation of the external genitalia of foetuses which are genetic males [37]. The explanation for this disturbed sex ratio is still obscure, although it was suggested [56] that it may be the result of a high abortion rate of males early in pregnancy since the smaller foetuses do not show this female preponderance; in a series of 6 anencephalic embryos lost in the first weeks of pregnancy the nuclear chromatin was negative and the gonads of 4 were testes although in the other 2 the differentiation of the gonad was insufficiently advanced to allow histological classification.

Chromosome imbalance has been thought to be the most likely cause of anencephaly [54, 69] and although chromosome studies have ruled out any gross abnormality, it does not necessarily exclude some minor imbalance such as a small translocation which cannot be detected by present techniques. However, LITT and STRAUSS [46] have reported monozygotic twins one of whom was normal and the other was anencephalic. Findings such as this would tend to support the view that anencephaly is due to factors other than genetic.

ACKOWLEDGEMENT

The author is indebted to Mr. J. R. McLean Keil for a grant for assistant for this investigation.

SUMMARY

1. A series of 13 male anencephalic foetuses and one normal male foetus for comparison were studied with regard to the development of the genital tract and the external genitalia, and the nuclear chromatin.

2. The age of the foetuses ranged from 10 weeks to 34 weeks.

3. The nuclear chromatin was studied in all foetuses and was found to be negative.

4. All anencephalic foetuses showed normal differentiation of the penis and scrotum.

5. Nine of the anencephalic foetuses, however, showed marked hypoplasia

of the normally differentiated external genitalia.

6. No evidence of partial sex reversal was seen and no evidence of abnormal persistence of the Müllerian ducts could be found.

7. X-ray of the skulls showed absence of the pituitary fossa in all 13 cases of anencephaly.

8. It was concluded that the normal differentiation of the male genital tract and external genitalia found in this investigation indicated normal foetal testicular function in anencephalic foetuses up to the 4th month.

9. It was also concluded that the hypoplasia of the external genitalia was due to a partial testicular deficiency occurring after the 4th month in anencephalic foetuses.

10. It was suggested that the cause of the partial testicular deficiency was due to the hypothalamic-pituitary lesion present in these foetuses and that the normal foetal testicular function present up to the fourth month was due to the high level of chorionic gonadotrophic hormone normally present up to this stage which compensated for the foetal pituitary deficiency.

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