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Comparative stereological studies on zonation and cellular composition of adrenal glands of normal and anencephalic human fetuses. II. Cellular composition of the gland

J. Bocian-Sobkowska[1], L.K. Malendowicz[2] and W. Woźniak[1]

[1]Department of Anatomy and [2]Department of Histology and Embryology, University School of Medical Sciences, Poznan, Poland

Summary. In our previous paper (Bocian-Sobkowska et al., 1997) we demonstrated a striking difference in development of zonation in adrenals of normal and anencephalic human fetuses. The purpose of the present study was to characterize, by means of stereology, the cellular composition of developing adrenals in the same case. Studies were performed on 11 pairs of adrenal glands from normal fetuses and 10 from anencephalic fetuses.

In the studied period of development (24 to 39 weeks of intra-uterine life) the average volume of cells in normal glands increased as follows: zona glomerulosa (ZG) from 355 to 870 μm^3; zona fasciculata (ZF) from 779 to 1200 μm^3; fetal zone (FZ) from 2004 to 2380 μm^3; and medulla (M) from 600 to 970 μm^3. In anencephalic fetuses, the appropriate values were: ZG - 380-680 μm^3; ZF - 460-680 μm^3; FZ - 1820-1680 μm^3; and M - 870-1400 μm^3. At the end of the studied period the number of ZG cells in normal fetuses was two fold higher than in anencephalics, ZF cells - 6-fold and in FZ - 5-fold higher, while in the M the number of cells was nearly equal in both groups. During the whole investigated period of intra-uterine development the total number of adrenocortical cells in normal glands increased ca 2.5-fold, while in anencephalic glands only ca 0.5-fold, reaching at the end ca 40% of normal value. In both normal and anencephalic adrenals the number of ZG and M cells was highly correlated with ZG/M cell ratio, being slightly higher in normal glands. No such relation was demonstrated for cells of the remaining adrenocortical zones.

Key words: Human fetal development, Adrenal gland, Zonation, Cellular composition, Normal human fetuses, Anencephaly

Offprint requests to: Dr. Joanna Bocian-Sobkowska, 6 Swiecicki St., 60-781 Poznan, Poland

Introduction

Anencephaly, a major congenital anomaly arising from defective development of the cephalic portion of the neural tube, provides a unique opportunity to study human adrenal gland development and function in the absence of the basal hypothalamus and pituitary gland. It is well documented that adrenal glands of anencephalic fetuses are notably smaller than those of normal fetuses and in some cases they are not found during autopsy (Keene and Hewer, 1927; Bernischke, 1956; Jost, 1966; Sucheston and Cannon, 1970; Gray and Abramovich, 1980).

The first systematic studies on the development of adrenal glands of normal and anencephalic human fetuses revealed striking differences in zonation of the glands (Bocian-Sobkowska et al., 1997). Development of the adrenal fetal zone (FZ) is the main factor responsible for prompt adrenal gland growth during the intra-uterine life (Bocian-Sobkowska et al., 1993). At the end of gestation the volume of that zone attains a size of over 8200 mm^3 and comprises 69-70% of the total gland volume, while respective values for zona glomerulosa (ZG), zona fasciculata (ZF) and medulla (M) are 1665 mm^3 (14%), 833 mm^3 (7%) and 1071 mm^3 (9%). These data are in striking contrast to those found in adrenals of anencephalic fetuses, in which volume of the gland attains only ca 35% of that in normal specimens. In the oldest anencephalic fetuses studied (39 weeks old) volume of the FZ was 962 mm^3 (ca 8-fold lower than in normal fetus), comprising only 25% of the total gland volume. For the remaining zones the values were: ZG - 1051 mm^3 (ca 90% of the normal value and 39% of the total gland volume); ZF - 770 mm^3 (ca 92% and 20% respectively); and M - 539 mm^3 (ca 50% and 14% respectively).

The purpose of the present study was to characterize, by means of stereology, the cellular composition of the

developing adrenal glands in normal and anencephalic human fetuses.

Materials and methods

Studies were performed on 11 pairs of adrenal glands from normal and 10 from anencephalic fetuses. Age, sex, crown-rump length (C.-R.L), body weight, and gross malformation of studied fetuses are detailed in our earlier report (Bocian-Sobkowska et al., 1997).

Adrenals were fixed in Bouin's solution, embedded in paraplast and cut at 5-6 μm. Transverse sections were taken from the middle part of the gland and stained with haematoxylin and eosin.

The first stage of the stereological studies (zonation of the adrenals) was performed according to Weibel (1979), as specified in our previous report (Bocian-Sobkowska et al., 1997).

In the second stage, the volume densities of nuclei and cytoplasm of the parenchymal cells and of stroma (connective tissue and blood vessels) and number of nuclear profiles per unit area were estimated on a screen at x3,000, using the multipurpose test system M42 (Weibel, 1979). From each adrenal gland the sections containing zona medullaris were chosen, and in these sections 100 test areas of the ZG, ZF, FZ, and M were counted. On the basis of earlier karyometric studies (Malendowicz, 1974), the shape - coefficient ß, which relates N_V to N_a and V_V, and depends on axial ratio of estimated nuclei, was assumed to be 1.382 for the ZF, FZ, M, and 1.500 for the ZG. The number of nuclei of parenchymal cells per 1 mm^3 was calculated according to Weibel and Gomez (Weibel, 1979). Since human adrenocortical and medullary cells are mononuclear, the numerical density of nuclei corresponds to the number of parenchymal cells. Subsequently, number of parenchymal cells in each adrenocortical zone and in the medulla, as well as in entire cortex, was computed. Results were expressed per adrenal pair.

The results were processed statistically and graphically by Origin programme for IBM PC AT.

Results

In the studied period of development (24 to 39 weeks of intra-uterine life) in normal fetuses the average volume of ZG cell increased gradually from 355 to 870 μm^3, while in anencephalic fetuses ZG cell volume increased up to the 31st week of fetal life (from 380 to 680 μm^3) and afterwards remained unchanged (Fig. 1). The number of ZG cells in normal fetuses exhibited an exponential increase at the end of the studied period, while in anencephalic fetuses this increase was very slow and at the end of intra-uterine life the number of cells in ZG of normal fetuses was ca 2-fold higher than in anencephalic fetuses of the same age (Fig. 2).

In normal fetuses the average volume of ZF cell gradually increased from 779 to 1200 μm^3, while in anencephalic fetuses the volume of these cells increased from 460 (24th week) to ca 680 μm^3 (29th week) and afterwards remained unchanged (Fig. 3). At the end of the 26th week the number of ZF cells was similar in both normal and anencephalic fetuses (ca $100x10^6$). Afterwards, in normal fetuses up to the end of gestation the number of ZF cells increased 6-fold, while in anencephalic ones it remained unchanged (Fig. 4).

During the whole investigated period, the average volume of FZ cell in normal fetuses ranged from 2004-2380 μm^3, while in anencephalic fetuses the average volume of FZ cell was lower and decreased slowly up to the end of the studied period (from 1820 to 1680 μm^3) (Fig. 5). In anencephalic fetuses the number of FZ cells remained unchanged up to the end of intra-uterine life, while in normal ones a gradual increase in the number of these cells was observed. As a result, the number of FZ cells in normal fetuses was 5-fold higher than in

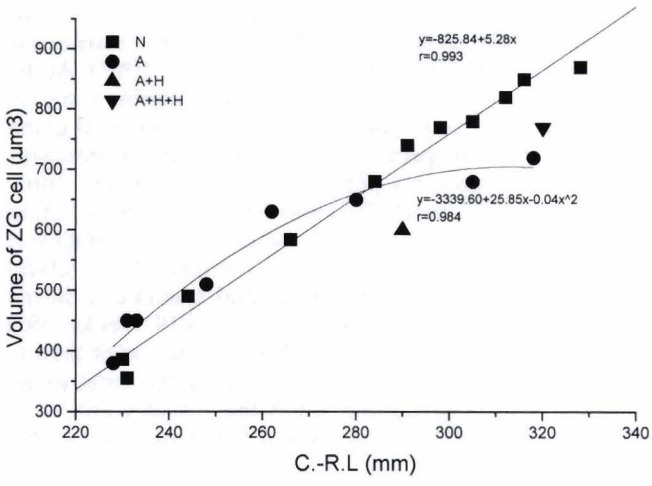


Fig. 1. Average volume of zona glomerulosa cell of adrenals of normal (N) and anencephalic (A) human fetuses. A+H: anencephalic fetus with hypophysis; a+H+H: anencephalic fetus with hypothalamus and hypophysis. C.-R.-L: crown-rump length. Each point presents one case.

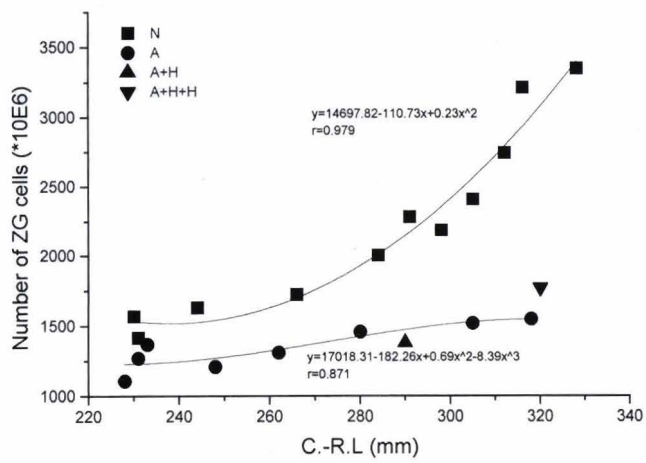


Fig. 2. Number of zona glomerulosa cells in adrenals of normal and anencephalic human fetuses. Explanations as in Fig. 1.

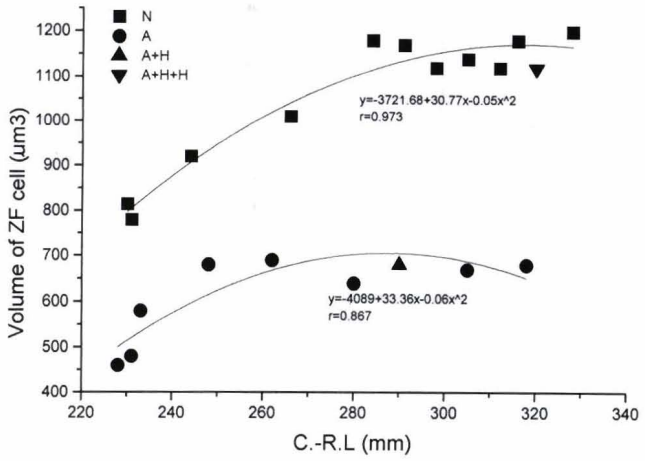


Fig. 3. Average volume of the zona fasciculata cell of adrenals of normal and anencephalic human fetuses. Explanations as in Fig. 1.

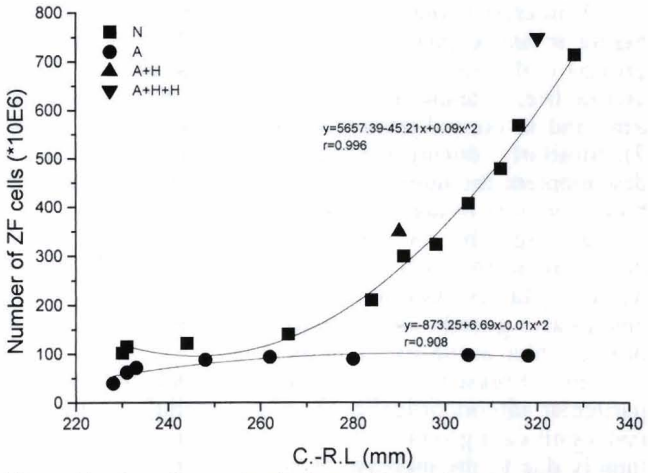


Fig. 4. Number of zona fasciculata cells in adrenals of normal and anencephalic human fetuses. Explanations as in Fig. 1.

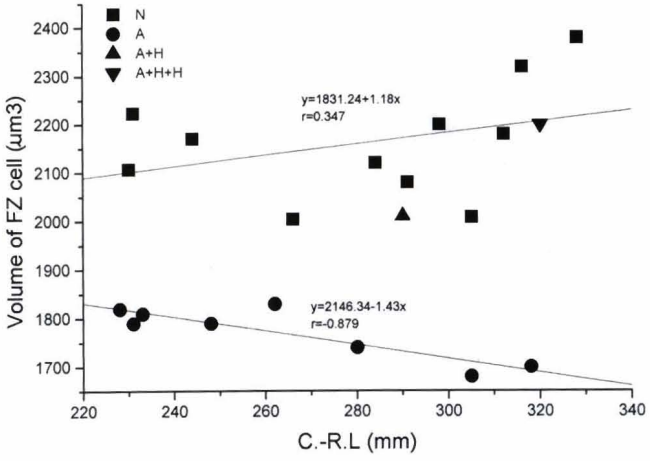


Fig. 5. Average volume of fetal zone cell of adrenals of normal and anencephalic fetuses. Explanations as in Fig. 1.

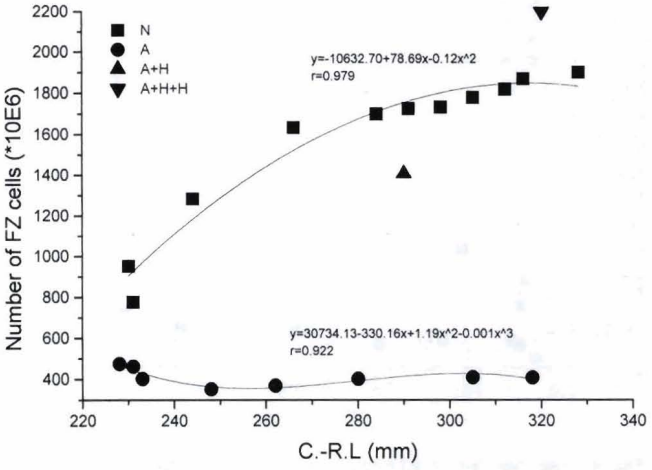


Fig. 6. Number of fetal zone cells in adrenals of normal and anencephalic fetuses. Explanations as in Fig. 1.

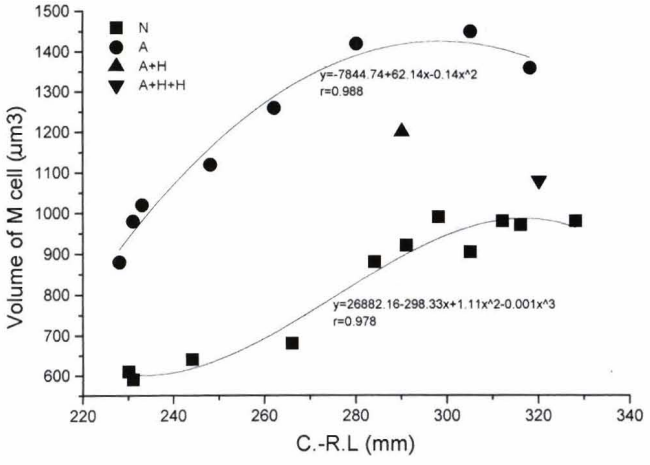


Fig. 7. Average volume of medullary cell of adrenals in normal and anencephalic fetuses. Explanations as in Fig. 1.

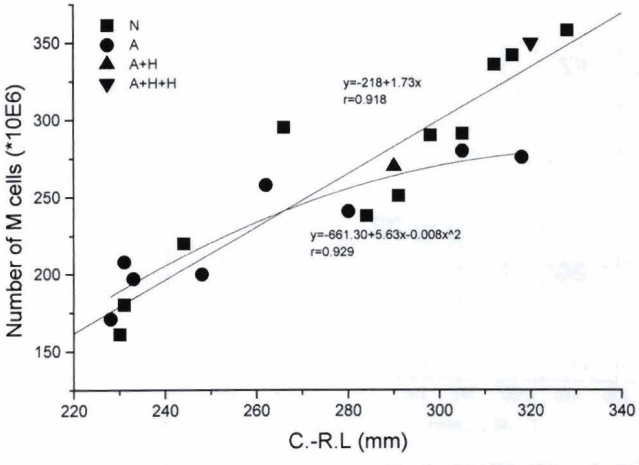


Fig. 8. Number of medullary cells in adrenals of normal and anencephalic fetuses. Explanations as in Fig. 1.

anencephalic fetuses (Fig. 6).

Of interest is that the average volume of M cell was higher in anencephalics than in normal fetuses. In both groups cell volume increased up to the end of intra-uterine life; in anencephalic fetuses from 870 to ca 1400 μm^3 and in normal ones from 600 to ca 970 μm^3 (Fig. 7). Similarly, during the whole investigated period of development the number of M cells was nearly equal in both groups of fetuses (Fig. 8).

During the whole investigated period of development the total number of adrenocortical cells in normal glands increased ca 2.5-fold, while in anencephalic glands only 0.5-fold, reaching ca 40% of normal value at the end (Fig. 9).

Fig. 10 presents distribution of parenchymal cells in particular adrenocortical zones and in medulla. A prompt and significant growth of adrenals of normal fetuses was mainly due to the increase in the number of ZG and FZ cells. Similarly, in anencephalic fetuses ZG and FZ cells were the most numerous. However, in the course of intra-uterine life their number increased only in a small degree.

Analysis of percentage distribution of parenchymal cells in adrenal cortex of normal human fetuses revealed that at the beginning of the studied period of development the ZG cells comprised ca 60% of all adrenocortical cells and that they then gradually decreased to ca 33%. On the contrary, the percentage of FZ cells increased from ca 35% to ca 65% (Fig. 11). In anencephalic fetuses, on the other hand, ZG cells comprised ca 70% of adrenocortical cells while FZ comprised about 20-22%. These values were rather constant in the whole studied period.

In both groups of human fetuses the ratio of the

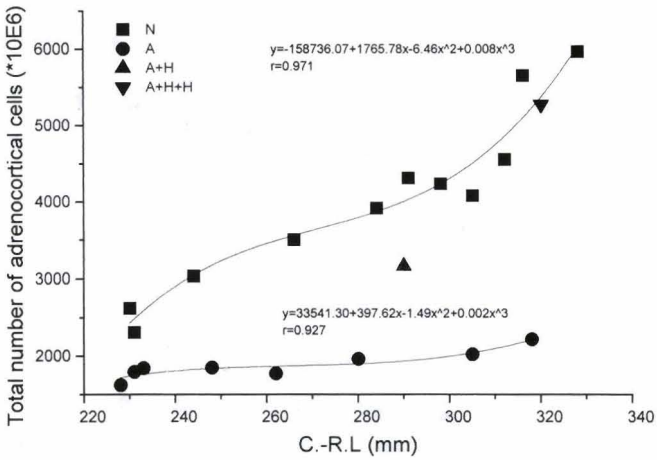


Fig. 9. Total number of adrenocortical cells in adrenals of normal and anencephalic human fetuses. Explanations as in Fig. 1.

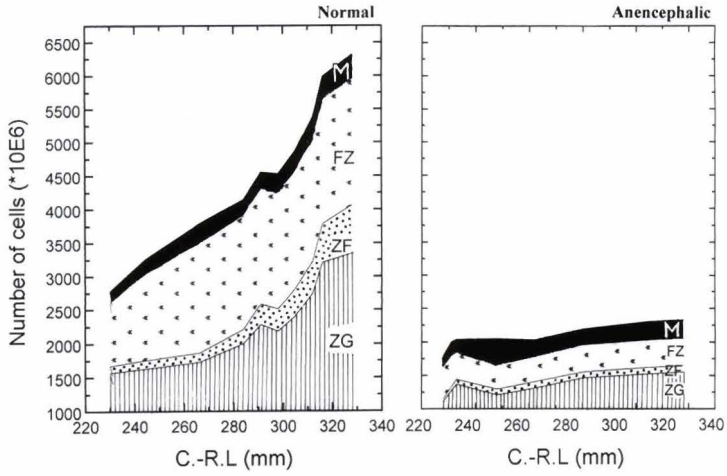


Fig. 10. Total number of adrenocortical and medullary cells and number of parenchymal cells in particular adrenocortical zones in adrenals of normal and anencephalic human fetuses. ZG-zona glomerulosa; ZF: zona fasciculata; FZ: fetal zone; M: medulla.

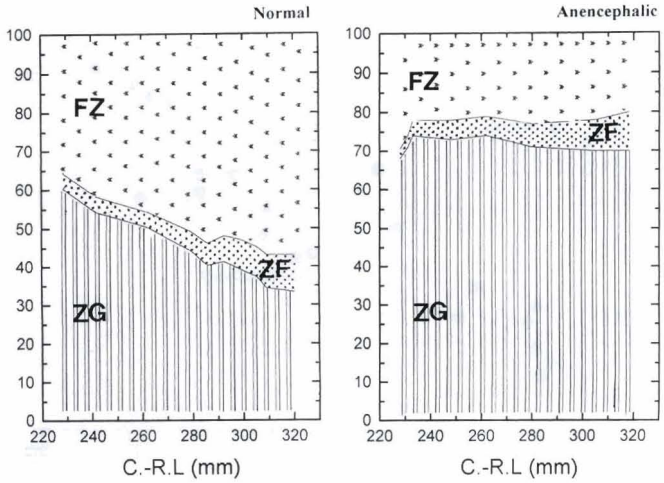


Fig. 11. Percentage distribution of parenchymal cells in particular adrenocortical zones in adrenals of normal and anencephalic human fetuses. Explanations as in Fig. 10.

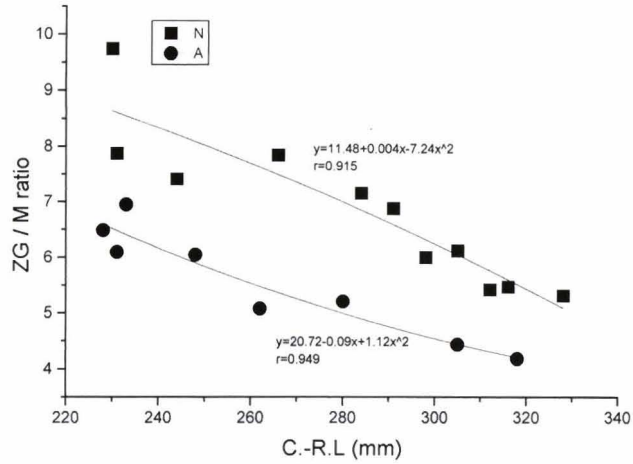
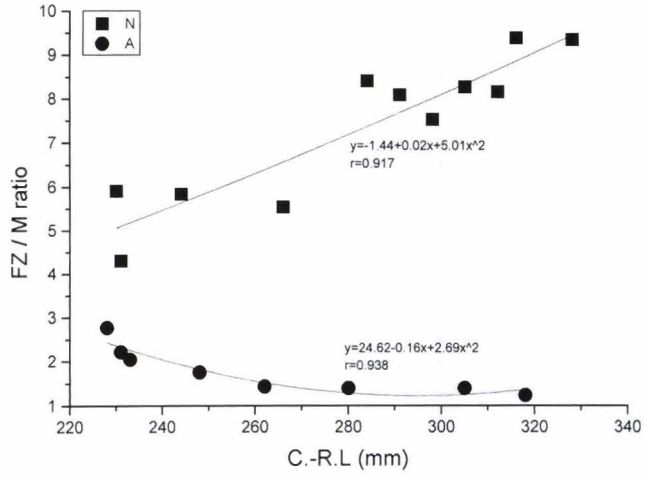


Fig. 12. Ratio of number of zona glomerulosa to medullary cells in adrenals of normal and anencephalic human fetuses. Explanations as in Fig. 1.



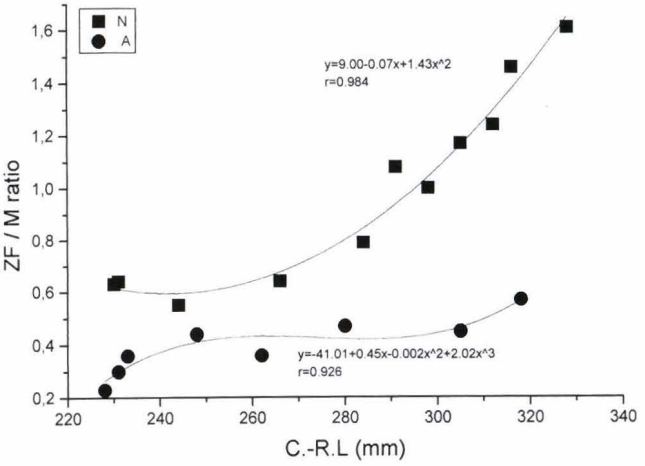


Fig. 13. Ratio of number of zona fasciculata to medullary cells in adrenals of normal and anencephalic human fetuses. Explanations as in Fig. 1.

number of ZG/M cells gradually and parallely decreased in the course of intra-uterine life, being slightly higher in normal adrenals (Fig. 12). On the contrary, ratios of the number of ZF/M, FZ/M, and total number of adrenocortical/M cells increased in normal fetuses and decreased or remained unchanged in anencephalic ones (Figs. 13-15).

Analysis of the stroma content (connective tissue and blood vessels) in developing human adrenal glands revealed than in the ZG and ZF of anencephalic fetuses it was nearly 2 times higher than in normal adrenals; in FZ, values were rather similar and in normal adrenals stroma fraction in M was about 2-fold higher than in

Fig. 14. Ratio of number of fetal zone to medullary cells in adrenals of normal and anencephalic human fetuses. Explanations as in Fig. 1.

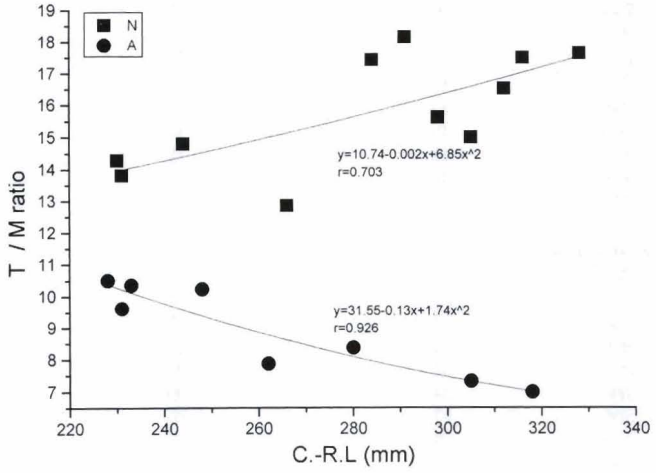


Fig. 15. Ratio of the total number of adrenocortical to medullary cells in adrenals of normal and anencephalic human fetuses in the course of intra-uterine life. Explanations as in Fig. 1.

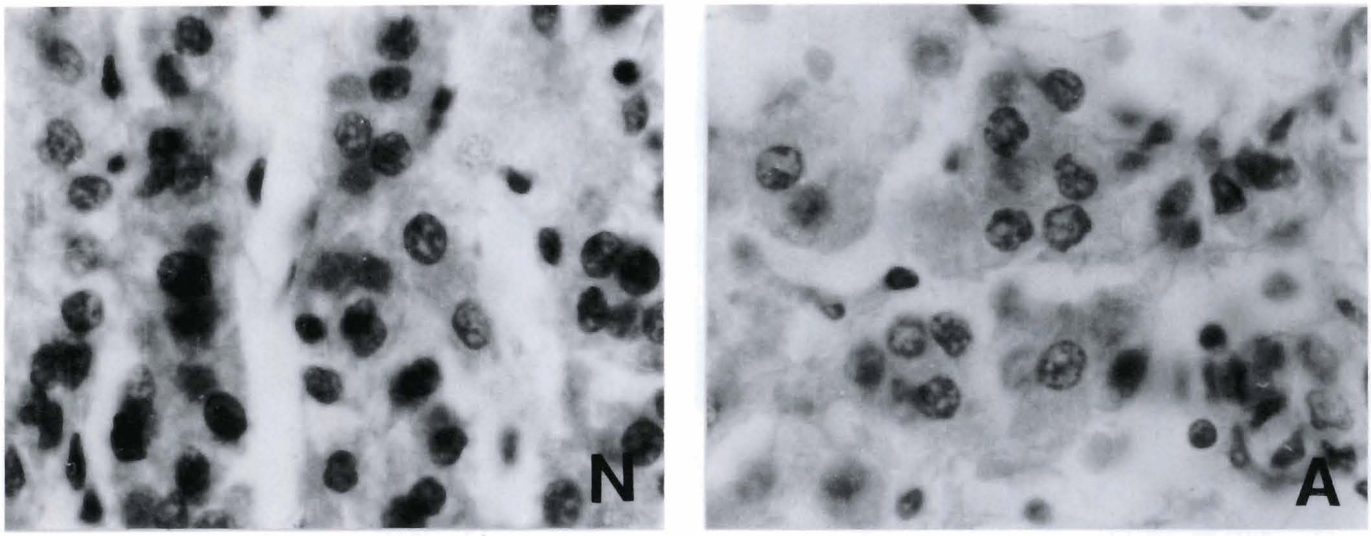


Fig. 16. Zona fasciculata of adrenal gland of normal (N) and anencephalic (A) human fetuses, 37-39 weeks of intra-uterine life. H+E. x 800

anencephalic fetuses (Table 1).

Fragments of ZF and FZ of normal and anencephalic adrenals are presented in Figs. 16 and 17.

Discussion

It is well known that until 16-20 weeks of intra-uterine period the development of the adrenal gland in anencephalic human fetuses is similar to that in normal ones. Afterwards, a rapid increase in adrenal weight and volume in normal fetuses contrasts with a slow development of the gland in anencephalic ones, in which, at the end of gestation, it attains only 35-40% of the mass of normal glands (Keene and Hewer, 1927; Bernischke, 1956; Jost, 1966; Sucheston and Cannon, 1970; Jost, 1975; Gray and Abramovich, 1980).

Our earlier studies (Bocian-Sobkowska et al., 1997) revealed differences int he development of adrenal gland zonation in normal and anencephalic human fetuses, while results of the present investigations explain the cellular basis of these processes.

Regarding the development of ZG in both normal and anencephalic human fetuses, linear increase in volume of the zone takes place and rates of growth are also similar (Bocian-Sobkowska et al., 1997). In the oldest cases studied, the volume of this zone attained 1665 and 1501 mm^3 in normal and anencephalic fetuses, respectively.

Detailed stereological analysis revealed a distinct difference in the structure of the zone in both studied groups. ZG of anencephalic fetuses contained 2-fold more stroma and only ca 50% of cells if compared with the normal gland. Despite this, during the whole studied period ZG cells comprised about 65% of all adrenocortical cells in anencephalic glands, while in normal glands this percentage decreased from ca 60% to 35%. This drop was mainly caused by notable proliferation of fetal zone cells in normal glands. Of interest is that in anencephalic gland ZG cells are the most numerous parenchymal cells of the cortex. This observation suggests that the control of proliferation and growth of the ZG in the course of intra-uterine life differs from mechanisms controlling the biological activity of the remaining zones. This difference has been recognized in numerous species of animals and indicates

Table 1. Volume fractions of stroma of particular adrenocortical zones in normal and anencephalic fetuses.

C.-R.L.	AGE IN POSTOVULATORY WEEKS	ZG	ZF	FZ	M
Normal					
231	24	0.09	0.05	0.14	0.26
230	25	0.10	0.06	0.14	0.27
244	26	0.11	0.05	0.16	0.25
266	29	0.11	0.08	0.15	0.30
284	31	0.11	0.08	0.16	0.31
291	32	0.12	0.10	0.16	0.29
298	33	0.12	0.11	0.17	0.28
305	35	0.12	0.10	0.18	0.32
312	36	0.14	0.12	0.17	0.36
316	38	0.15	0.10	0.19	0.38
328	39	0.15	0.16	0.18	0.40
Anencephalic					
228	24	0.10	0.15	0.16	0.13
231	25	0.16	0.17	0.17	0.14
233	27	0.16	0.18	0.16	
248	28	0.20	0.20	0.17	0.16
262	32	0.24	0.27	0.19	0.16
280	34	0.24	0.30	0.18	0.18
305	37	0.26	0.35	0.18	0.18
318	39	0.30	0.37	0.20	0.20
290*	34	0.17	0.12	0.18	0.16
320**	38	0.15	0.14	0.20	0.36

*: anencephalic with hypophysis; **: anencephalic with hypophysis and hypothalamus.

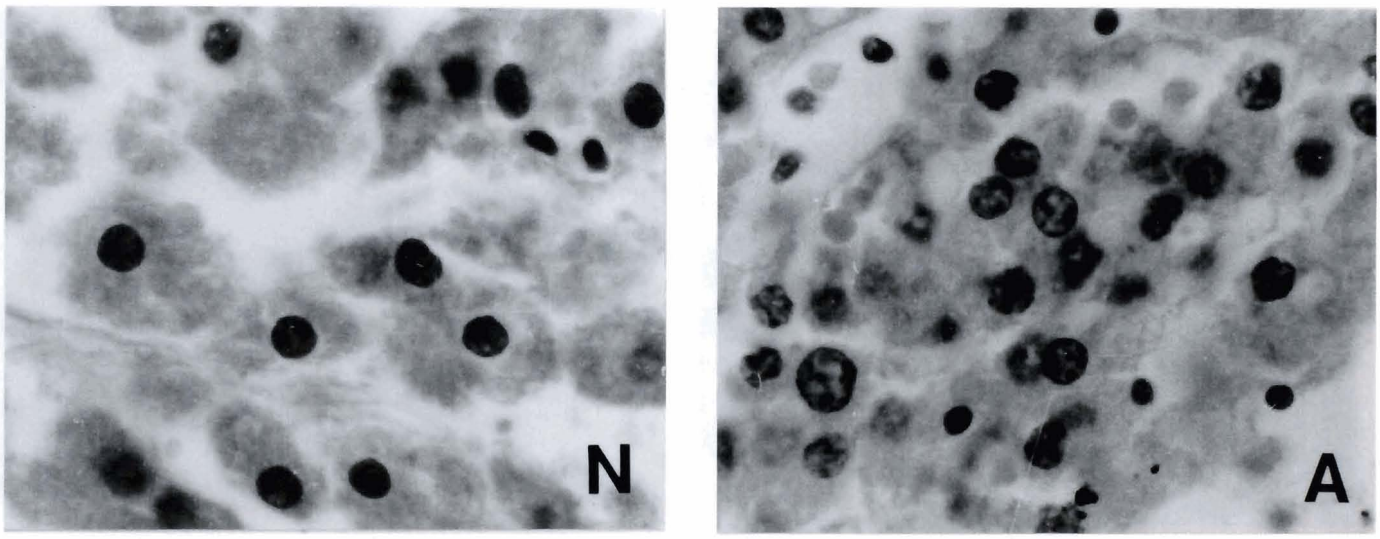


Fig. 17. Fetal zone of adrenal gland of normal (N) and anencephalic (A) fetus, 37-39 weeks of intra-uterine life. H-E. x 800

autonomous, rather ACTH-independent growth of the ZG (Nussdorfer, 1986; Vinson et al., 1994).

Regarding ZF development in both normal and anencephalic fetuses, the volume of this zone increased nearly 8-fold (Bocian-Sobkowska et al., 1997). However, in normal adrenals fasciculata cells were notably larger. It has to be pointed out that in anencephalic fetus with hypophysis and hypothalamus the average volume of ZF cell was similar to that of normal fetuses, while in the second case, in which only hypophysis was found, the size of fasciculata cells was similar to that in other anencephalics. These findings suggest that proper development of the ZF in adrenals of human fetuses requires the presence of an operating CRH-ACTH system, which is also responsible for proliferation of fasciculata cells. Since, in the ZF, fraction of stroma increased during the whole investigated period from 5% to 16% in normal, and from 15% to 37% in anencephalic fetuses, it seems legitimate to suggest that development of this component of the gland is independent of CRH-ACTH system. Moreover, this finding seems to suggest that in the course of ZF development the amount of stroma (connective tissue and blood vessels) is not correlated with either ZF cell volume or the number of fasciculata cells. In studied fetuses ZF forms a narrow band of cells which frequently send fingerlike projections of cells into the outer rim of the fetal zone, from which they are separated by sinusoids, scanty in normal fetuses, and abundant in anencephalic ones.

Some authors describe the developing ZF as a transitional zone between the fetal and definitive (ZG) zones (Sucheston and Canon, 1968; McNutt and Jones, 1970). According to Mesiano and Jaffe (1992) cells of this zone have the capacity to synthesize cortisol.

The development of the adrenal fetal zone is the main factor responsible for normal adrenal growth during intra-uterine development (Gray and Abramovich, 1980). At the end of the fetal period the volume of this zone attains a size of over 8200 mm^3 constitutes 67-70% of the total gland volume in normal fetuses, while in anencephalic fetuses the volume of this zone is ca 8-fold lower and comprises only 25% of the total gland volume (Bocian-Sobkowska et al., 1997). As expected, the present study reveals larger cells of the FZ in normal fetuses. Moreover, these cells are 5-fold more numerous than in adrenals from anencephalic fetuses, in which the quantity of these cells remains practically unchanged throught the whole investigated period.

Until the fifth month of intra-uterine life the development of the fetal adrenal cortex depends on maternal placental factors, presumably human chorionic gonadotropin (hCG) and/or placental adrenocorticotropin (ACTH), while in the second half of pregnancy the fetal ACTH is the main factor responsible for proliferation and growth of the gland (Jost, 1966; Fisher, 1986). As reviewed by Mesiano and Jaffe (1992) the tropic action of fetal ACTH on developing adrenal glands is mediated by locally expressed growth factors, of which epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor II (IGF-II) are the most important in stimulation of fetal-adrenal growth. This contention seems to be proven by findings of Abu-Hakima et al. (1987) who demonstrated a lack of ACTH effect on ^{3}H-thymidine incorporation into cultured fetal adrenal cells obtained from normal glands at 13-15 weeks of gestation. On the contrary, administration of ACTH into human anencephalic fetuses in utero restores their adrenals to the size of normal glands, with well developed FZ (Johannisson, 1968; Honnebier and Swaab, 1973). As far as the pituitary-adrenocortical function in anencephalic fetuses is concerned, Allen et al. (1974) demonstrated that their adenohypophyses contain a readily dischargeable pool of ACTH. The absence of the hypothalamus seems to be responsible for the lack of ACTH secretion in anencephaly. Moreover, acute stimulation of endogenous ACTH secretion or corticotrophin administration did not result in the expected secretory response by its target organ in anencephalic fetuses, presumably due to atrophy of the adrenal cortex.

It is well documented that the fetal human adrenal gland operates within the fetal-placental unit (Diczfalusy, 1969), and that its secretory pattern is quite different from than in adults. Briefly, fetal adrenal cortex due to a lack of 3ß-hydroxysteroid dehydrogenase (3ßHSD) does not synthesize large amounts of pregnenolone and progesterone. Activity of 3ßHSD develops just before delivery or at birth, while during the intra-uterine life an expression of this enzyme is suppressed by the placental estrogens (Neville and O'Hare, 1982; Winter, 1985; Branchaud and Murphy, 1992). Moreover, in human fetal adrenals 18-hydroxylase and 18-steroid dehydrogenase activities are absent and therefore fetal adrenals do not synthesize aldosterone (Goldman et al., 1966; Solomon et al., 1967). On the contrary, the fetal adrenal express very active sulphokinase, responsible for steroid ester sulphates, mainly dehydroepiandrosterone (DHEA) sulphate, synthesis. Cholesterol side-chain cleavage enzymes and 3ßHSD are present in the cytotrophoblast and the placenta, as is known, produces large amounts of pregnenolone and progesterone, from both endogenous cholesterol and LDL (Carr and Simpson, 1981). These steroids, via the umbilical vein reach the fetal adrenal where they undergo further transformations into corticosterone, cortisol, and mainly DHEA sulphate. In the placenta, this last compound, after the splitting of sulphate ester linkage and subsequent oxidation, is transformed into androstenedione and testosterone which are rapidly aromatized to estrone and estradiol. There are suggestions that the fetal zone is present only in those mammalian species in which placental cytotrophoblast has a very high aromatizing activity (Ainsworth and Ryan, 1966; Bloch, 1968; for review see Nussdorfer, 1986). Also, some authors (Neville and O'Hare, 1982; Winter, 1985; Branchaud and Murphy, 1992) claim that the presence of the fetal zone is dependent on inhibition

of 3ßHSD by placental estrogens.

In vitro studies of separated fetal zone show that in response to ACTH the FZ cells produce large amounts of DHEA sulphate and little cortisol (Seron-Ferre et al., 1978).

An in situ perfusion study showed that neither acetate nor free cholesterol was efficiently converted into steroids by the human fetal adrenal (Solomon et al., 1967). ACTH increased the number of LDL-cholesterol receptors and the rate of LDL degradation by fetal adrenal cells (Carr et al., 1980). Cited authors suggest that the low, not stimulated by ACTH, binding of LDL-cholesterol to anencephalic adrenals is due to the low exposure of the gland to ACTH in utero. However, the rate of de novo cholesterol synthesis in anencephalic adrenals, although lower than normal, due to diminished 3-hydroxy-3-methylglutaryl coenzyme A reductase activity, is stimulated by exposure to ACTH in vivo. These findings suggest that the novo synthesized cholesterol is the main substrate for steroidogenesis in adrenals of anencephalic fetuses.

In an earlier study we demonstrated an exponential increase in the volume of adrenal medulla of normal fetuses from 329 to 1071 mm^3 (9.5-9.0% of the gland volume) which contrasted with a low linear growth of that zone in anencephalic fetuses (173 to 539 mm^3; 10-14%, respectively) (Bocian-Sobkowska et al., 1997). Present investigations revealed that the average cell volume of medullary cells was larger in anencephalic fetuses, reaching about 1400 μm^3 at the end of fetal life, as compared to normal fetuses where it was about 970 μm^3. On the other hand, the number of M cells was similar in both investigated groups, and increased at the end of the studied period. The percentage of stroma was higher in normal than in anencephalic fetuses, comprising about 40% and 20%, respectively in the oldest cases, which is in agreement with our earlier report. Chromaffin cells were arranged in characteristics whorls between adjacent sinusoids or formed round and ovoid groups (Bocian-Sobkowska et al., 1996).

The adrenal medulla is derived from sympatho-adrenal progenitors originating from the neural crest, which migrate to adrenal primordium during embryonic period (Landis and Patterson, 1981; Anderson and Axel, 1986; Unsicker et al., 1989). Glucocorticoids are essential for the differentiation of sympathoadrenal progenitors into catecholamine-producing cells by the induction of phenylethanolamine-n-methyltransferase (Michelsohn and Anderson, 1992; Anderson, 1993). In the anencephalic fetuses with insufficient glucocorticoid production this differentiation is disordered and the medullary cells are larger, although their number is similar to that in normal fetuses. The lack of sufficient glucocorticoid production may be related to the incidental neuroblastoma found in the adrenal gland of an anencephalic fetus (Van Hale and Turkel, 1979).

Numerous experimental data indicate that the adrenal medulla exerts a paracrine control on the secretory activity of the cortex, especially on its zona glomerulosa (for review, see Hinson, 1990; Malendowicz, 1993; Vinson et al., 1994). The main substances involved in this process are catecholamines and numerous biologically active peptides that may act either directly on adrenocortical cells or on vasculature (Vinson et al., 1994). In addition to numerous cortical adrenergic and peptidergic nerve fibers of medullary origin, this paracrine regulatory function may be exerted by the chromaffin cells, which are intermingled with adrenocortical cells, especially in the zona glomerulosa (Bornstein et al., 1994). Regarding this interaction, the present study demonstrates that in both normal and anencephalic adrenals the number of zona glomerulosa to medullary cells was highly correlated. In normal adrenals the ratio of the number of zona glomerulosa to medullary cells was slightly higher than in anencephalic adrenals, and in both groups its value decreased toward the end of the fetal period. No such relation was demonstrated for cells of the remaining adrenocortical zones, thus emphasizing the importance of mutual interrelationship between zona glomerulosa and medullary cells in the developing human adrenal gland.

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