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**Anencephaly
Geographic Incidence, Etiology and Hormonal Relations
of the Pituitary and Adrenal Cortex**

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**Anencephaly:
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Introduction

Anencephaly, so far at least, has not been attributed to hormonal imbalance. It has, however, recently become apparent that a hormonal imbalance between the fetus and pregnant mother does arise as a result of the abnormality. There is a paucity of information about hormonal relations in the anencephalic newborn, because of infrequency of the condition and short life span of the infant. Only a few hormonal studies exist, but there is a considerable literature about the two main anatomic deficiencies, viz., the deficient pituitary and atrophic adrenal glands. This chapter will consider a few of the more important studies and will mention some unpublished observations of the author.

Historical

Anencephaly is abundantly described and discussed in early medical history. This malformation enjoys one distinct advantage unique in medicine, i.e., it cannot be misdiagnosed! The infant in Fig. 1 was described by LYCOSIENNEK [30] in 1557. He writes:

Quinto Calend. Septembris, Argentina nobilis Alfatice
metropoli, infans femineo sexu, horrendo, inglorio, atque
insuperiori parte aperto plane capite, laevore, bouinis oculis,
naribus aquilinis natus est.

Translation: In the month of September, it is known an infant of female sex was born in Strassbourg, the metropolis of Alsace, a

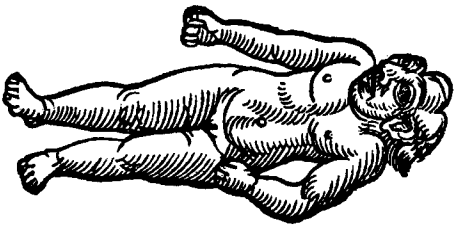


Figure 1. Anencephalic monster born in Alsace during reign of Charles V. (Courtesy Genesling Medical Library, Historical Collection).

horrible monster and with the head for the most part completely open, the mouth wide with eyes like an ox, and with nostrils like an eagle. MOROGONI [37] described three cases of anencephaly; he did not comment on the pituitary, but stated that the abdominal viscera were normal. ZANDER [55] in 1890 firmly established the fact that the adrenal glands are small in anencephaly.

Geographic Incidence

Despite certainty of diagnosis and the fact that anencephaly is relatively common among congenital CNS malformations, most physicians deliver only very few women of such infants, if any, during a life time. Students of the problem, therefore, have to obtain their cases for study from colleagues, hospital records, and government registrars. Adequacy of statistical data depends obviously upon the curiosity and

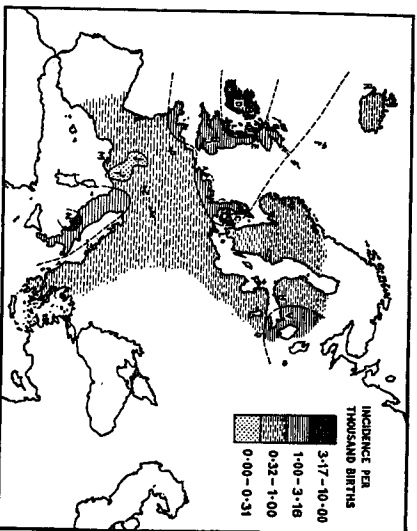


Figure 2. Distribution of anencephaly in Europe based on births in hospital (After Parsons, with permission editor J. med. Dict. Res.).

thoroughness of the medical profession in addition to a government with an enlightened outlook towards public health. The degree of completeness of birth and death certificates of different countries varies widely. This eliminates many areas of the world as a source of data for study of anencephaly.

Recent studies show that the incidence varies widely in different areas at the same time and in the same area at different times. Thus, BOOX and FRACCARO [8] and PEARSON [47] analyzing an extensive literature report that the incidence in Ireland (Belfast [0.67%] and Dublin [0.50%]) is three times higher than in Birmingham, England, (0.23%) and ten times higher than in Malmsö and Lund, Sweden (0.063%), and 50 times higher than in Lyons, France (0.012%). Indeed, COPPEY and JASSON [12] find variation among hospitals in Dublin. During 1940-1949 there appears to have been a decrease in incidence in Scotland and Birmingham. These data concerning the incidence in the British Isles are significant, because the social

and economic standards are parallel and the medical profession is homogeneous. It has been further reported [1] that in comparable North American populations the incidence in Charleston, South Carolina (0.061%), is less than one-half that of Halifax, Canada (0.15%), which is 1000 miles north. Table I from Penrose gives the numerical ratios for 33 medical centers with geographic distribution as shown in Fig. 2. Any theory of etiology will have to take into account this remarkable distribution as well as the fact that most anencephalic infants are born in winter (December), having been conceived in early spring. It is worthy of note that distribution of hydrocephaly parallels that of anencephaly but the sex ratio is about equal for hydrocephaly while anencephaly affects the female three to five times as often as the male. Despite the staggering effort represented in the foregoing data, the actual incidence of anencephaly is unknown because many such conceptions are aborted, frequently without knowledge of the patient. The high incidence of malformations in abortions is well known.

Etiology

Study of possible transmission of the malformation is made difficult, because affected infants do not live to reproductive age. However, there is a 2-3% risk of central nervous system malformation in subsequent children of the same parents having a child with anencephaly. This is more than six times the risk in the general population and suggests strongly a genetic influence. There are some examples of both monozygotic twins having the defect, but there are more examples of one of a pair of monozygotic twins having the defect and the other twin being normal. Obviously such a case is due to other than genetic influence. Anencephaly has its highest incidence in mothers of blood type O. The high ratio of female to male anencephalics is almost unique among congenital abnormalities although there is a similar trend in patent ductus arteriosus and congenital dislocated hip. Anencephaly is the only malformation with a high seasonal incidence. This is especially pronounced in Europe but not in North America. Björkvaars [16] has suggested that the absence of seasonal variation in United States is due to the "deepfreezer" eliminating seasonal swings in diet! This is doubtful but, if so, the change could be detected in birth rate before an after World War II. If one considers the fact that gestation of the anencephalic is usually 2-3 weeks shorter than the usual 9

Table I
Incidence of anencephaly among infants born in hospital (after Penrose)

Area	Period	No. births	Anencephalics No.	%
<i>Europe</i>				
London	1938-53	52,693	82	0.156
Birmingham	1940-47	138,907	366	0.229
Liverpool	1923-52	13,964	44	0.315
Belfast	1938-55	30,855	207	0.671
Dublin	1931-54	12,552	63	0.502
Copenhagen	1917-46	107,840	170	0.101
Malta and Land	1917-46	17,082	67	0.063
Helsinki	1935-44	11,424	34	0.229
Vilnius	1928-37	10,655	117	0.064
Reykjavik	1949-55	141,706	27	0.054
München	1929-41	49,539	65	0.012
Zürich	1921-44	144,611	7	0.005
Paris	1945-55	59,406	36	0.400
Lyon	1943-51	8,228	12	0.145
Napoli	1938-47	7,991	1	0.013
Palma	1949-55	12,969	10	0.078
Torino	—	—	21	0.060
Barcelona	1951-55	34,978	—	—
<i>North America</i>				
Rhode Island	1936-52	168,654	326	0.194
Boston, Mass.	1930-41	28,024	67	0.231
Rochester, Minn.	1944-50	8,716	5	0.057
London, Ont.	1945-55	10,834	12	0.111
Montreal, Q.P.	1950-55	19,839	42	0.211
Charleston, S.C.	1946-55	55,156	34	0.061
Halifax, N.S.	1946-55	49,704	74	0.150
<i>Africa</i>				
Johannesburg (A)*	1951-55	32,186	6	0.019
Pretoria (A)*	1953-55	4,407	1	0.023
Johannesburg (E)*	1952-53	7,779	6	0.077
Pretoria (E)*	1953-55	8,413	8	0.095
<i>Asia</i>				
Bombay	1946-55	76,763	58	0.076
Singapore	1953	8,287	8	0.097
Hong Kong	1951-53	52,116	18	0.056

* (A) Native African, * (E) European

months, then, the environmental influence would be acting during mid-summer. Taking into account distribution, familial incidence, seasonal incidence, frequency in pairs of twins, and sex ratio, a genetic factor cannot be invoked with precision.

From studies of COFFEY and JESSOP [11], a strong suggestion of an environmental influence is derived. These Dublin investigators found the malformation more common in the lower socio-economic class of patients who have a higher incidence of minor illnesses, such as 'colds'. Indeed, they found that by eliciting a history and by serological examination of blood drawn for this purpose in a prospective study, a large number of mothers of anencephalic infants had Asian influenza in the early weeks of gestation. Their analysis of the incidence following the 1957-58 Asian influenza epidemic showed a marked increase in rate of anencephaly which coincided with maternal illness during the first trimester of pregnancy and also in women with positive serological evidence who had no clinical history of influenza.

Experimental Production

Exencephaly (incomplete eversion of the brain) has been described as occurring with high frequency in some strains of mice and in offspring of some strains of X-irradiated male mice. Anencephaly is readily induced in offspring of pregnant mice and rats by X-irradiation. Pantothemic acid deficiency induces complex cranial abnormalities including anencephaly as do vitamin E and folic acid deficiencies. Anoxia causes anencephaly in mice and birds. Excess of CO₂ is even more effective. Other chemical agents include tryptoflavine, spiroin, trypan blue, ricin, salicylates, actinomycin, and oral hypoglycemic agents. Excess of vitamin A seems to be the most reliable method for production of anencephaly in rats and mice. All of these agents seem to act best about the time of gastrulation, i.e., 8-10 days gestation. The human embryo is said to be most sensitive to X-irradiation at about 16-18 days of gestation. These experimental methods of producing anencephaly have been tabulated by GRENOLD [21]. JOST [26] has devised an elegant technique for decapitating the head of the rabbit fetus *in utero*. This results in atrophy of the peripheral endocrines but is not quite comparable to anencephaly in the human. HUTCHINSONS *et al.* [23] failed to cause peripheral endocrine atrophy by destroying the hypophysis of the monkey fetus *in utero* during the last month of pregnancy.

Pathogenesis

The morphogenesis of anencephaly is unsettled. One prominent school, usually cited in textbooks of embryology, holds that the defect arises from failure of the anterior neural tube to close. Ordinarily closure is about the 3-4 mm stage (3rd week) before subdivision into forebrain, midbrain, and hindbrain. Yet anencephalics have well-developed eyes and cranial nerves suggesting the defect arises later. Another school holds that spinal fluid dynamics are upset, from possible stenosis of the aqueduct, resulting in development of a condition of internal hydrocephaly with subsequent degeneration of forebrain and midbrain. If one assumes absence of brain tissue causes loss of stimuli for bone development, this would explain the varying stages of vault formation found in different anencephalics.

Rapid growth and complex folding in early formation of the brain is well-known and any interference at this time would have catastrophic consequences. PATTEN [46] recently described several embryos in which there was asymmetry and overgrowth of the early formative roofplate and parts of the fore and midbrain. This is frequently seen in aborted specimens and is usually ascribed to artifacts and poor fixation, but he is convinced that it is a developmental defect which may give rise to anencephaly. Elongation of the neural tube appears to depend on stretching produced by growth of adjacent tissues, especially the notochord. It has also been postulated that anencephaly results from lack of mechanical tension, because of impeded growth of the chordal system. Another prominent view [54] is that developing arteries from the carotid and vertebral systems fail to organize properly, invade the *in situ* vascular bed of the encephalon, and assume the pattern destined for adult distribution. Brain formation may be partly influenced by embryonic blood vessels somewhat like embryonic bone formation is influenced by early vascularization. The angiomatous mass found at term may be the remnant of earlier vascular non-organized encephalon.

Anatomy

a) The Lesion

Examination of an anencephalic infant reveals that the scalp and frontal bones above the supraorbital ridge, the parietal bones, and usually the squamous portion of the occipital bone are absent. The

foramen magnum may be incomplete and the spinal canal partially or completely open, in such cases the term *interecephaly* may be applied. The anterior fossa is foreshortened, the sphenoid bone flattened, the clinoid processes are frequently absent, and the sella shallow or non-existent. Cerebral hemispheres, basal ganglia, and hypothalamus are absent. The medulla is frequently present in an imperfect form, and the cerebellum is usually absent but when present is markedly imperfect. The bones of the base of the skull are covered with a highly vascular meshwork of mesenchymatous tissue in which are sometimes found varying amounts of cerebral tissue, disorganized neurones, glia, choroid plexus, and, very rarely, cranial nerve nuclei. This mass of red-purple tissue varies in thickness from a few millimeters to a few centimeters and lies directly on bone, dura being absent. The mass is sometimes partly covered by hair-bearing squamous epithelium, but is usually nude with the exposed surface condensed into a relatively acellular collagenous membrane. This becomes the seat of infection if the infant lives a few days. Fragments of cranial nerves may be found in various foramina, and if rachischisis is absent, spinal cord is present. Rarely may fragments of cerebral tissue be found in the meninges. The eyes bulge forward because of foreshortened orbits giving the characteristic frog-like appearance in wood-cuts of medieval illustrators. In about a third of the cases the bony defect extends varying lengths into the spine and in these instances some cervical vertebrae may be absent so the chin lies at the level of the sternum. In such cases, the thoracic cavity is reduced in size with less space available for the heart and lungs. Concomitant lesions include: talipes equinovarus or valgus, spina bifida, cystic kidneys, cystic liver, high palate with frequent cleft, diaphragmatic hernia, 'immature' lungs with cuboidal cells lining the alveoli, polydactyly, megaloesophagus, hypertrophy of the bladder, deficient Auerbach and Meissner's plexi, thymic hyperplasia, degeneration of retinal ganglion cells and hypoplastic epiphyseal epiphyseal [56].

b) Pituitary

The anterior pituitary is rarely of normal size, and often on cursory examination said to be absent. However, laborious search with serial sectioning of the sella region will always reveal at least a few scattered clumps of anterior pituitary cells [2]. Cytologic study of these cells by the now elegant tinctorial techniques for differentiation has not been done. Figure 3 shows a pituitary which weighed 90 mg. This is the largest pituitary known to the author from a case of anencephaly, yet the

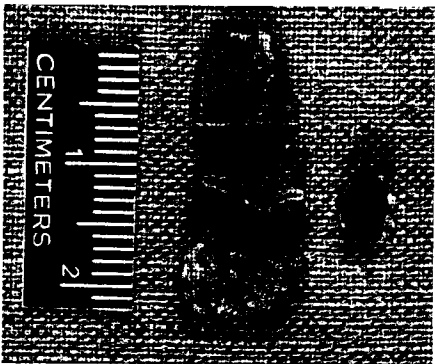


Figure 3. In this case of anencephaly the pituitary gland at the top consists entirely of normal anterior lobe tissue with vascular stasis. It weighs 90 mg, being the greatest amount of pituitary tissue in anencephaly known to the author. ACTH assay was not done. The adrenal beneath shows atrophy characteristic of anencephaly (Courtesy Dr. DAVID JASTINE).

adrenals show the usual atrophy. Microscopic examination (with hematoxylin and eosin) showed considerable vascular stasis and well-preserved parenchyma, not unlike that of a normal newborn. The posterior lobe is usually absent, but when present is separate from the anterior lobe. Of course, the hypophysal portal system and hypothalamic connections do not exist. Figure 4 shows a sagittal section of sphenoid bone from an anencephalic with a histologically 'normal' anterior pituitary at the base of the cranio-pharyngeal canal. Disregarding shrinkage, calcifications from measurements on the slide indicate this gland would have weighed 56 mg, yet the adrenals in Figure 5 are atrophic.



Figure 4. Note the die-like pituitary on the pharyngeal surface of the sphenoid bone immediately beneath the persistent cranio-pharyngeal canal. In the gross it measured 6 mm in diameter and $1\frac{1}{2}$ -2 mm in thickness. The wedge of free tissue anteriorly is an aberrant fold of nasal mucosa. Magnification 13x (after Nichols *et al.*, with permission of the Endocrine Society).



Figure 5. Adrenals on left from a full-term 'normal' infant dying two hours after birth with adrenocortical atrophy (combined weight 7.2 grams). These glands consist mainly of fetal zone. Adrenals on right are from same as pituitary in Figure 4. The fetal zone is entirely absent, and the cortical tissue present is the rim of definitive cortex characteristic of adrenocortical atrophy (combined weight 0.29 grams) (after Nichols *et al.*, with permission of the Endocrine Society).

e) Adrenal Gland

The adrenal cortex arises at a level between the seventh cervical and second thoracic nerves from ectoderm contiguous and continuous with its caudal gonadal anlagen. At about the 8 mm (crown-rump length) stage or 4 weeks of gestation a wave of cells migrates from each lateral primordium to a position adjacent to the root of the dorsal mesentery. This first migration of cells forms the 'fetal zone' and is immediately followed by a second wave which forms the 'definitive zone'. At about the 20 mm stage phochromoblast cells begin migrating to invade the cortex and form the medulla; this is complete at about the 10 centimeter stage. The adrenal glands of the normal fetus in proportion to other organs are comparatively larger about the 4th month of gestation than at any other time in life. The cortex of the gland at this time is composed of definitive and fetal zones; the latter predominates and reaches its apex at time of birth. The medulla at birth is negligible.

The definitive zone is composed of a few layers of small uniform well-differentiated cells having nuclei and cytoplasm that stain prominently basophilic with hematoxylin and eosin. It is located just beneath the capsule, and a few months after birth differentiates into the zona glomerulosa, zona fasciculata, and zona reticularis of the adult. The fetal zone immediately begins involution at birth and is sometimes accompanied by hemorrhage. This zone is confined to the human, monkey [28], and perhaps, the armadillo [38]. It composes most of the gland in the newborn, is just beneath, and is much thicker than the definitive zone. The cells are large, having an indistinct slightly eosinophilic cytoplasm, and a small nucleus which stains poorly with hematoxylin and eosin.

The definitive and fetal zones of the human were first described in a series of five papers by the Polish workers SZARZYNSKI and WIGURZYNOWSKI [51] in 1918. ELLIOT and AMOUR [17] in 1911 observed that adrenal glands of the newborn adrenocortical were devoid of fetal zone. This observation has been confirmed repeatedly in all of the world's literature and exceptions noted by only four authors [20, 34, 52, 22]. All of the cases are not convincing. In an effort to determine the magnitude of this atrophy a normal adrenal weighing 4.9 g from an infant dying one hour after birth was cut serially to yield 1280 sections. Every fifth section [256] was projected onto paper at 30 diameters magnification. The definitive zone and fetal zone with medulla were traced, cut out and weighed as previously described

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usually is given only

Table II

Weight of a 'normal' adrenal from a newborn compared with weights of three adrenals from cases of term anencephaly. The proportion of definitive and fetal zones has been determined by projection of serial sections and the mass of these zones determined. It can be seen that the definitive zone undergoes almost as profound atrophy as does the fetal zone.

Weight of gland	'Normal' Adrenals from three cases of anencephaly		
	A adrenal from newborn	B decrease	C decrease
4.9 grams	246 mg 95%	283 mg 94%	124 mg 97%
Definitive of gland actual mass	portion 13%	75.7%	87.3%
	0.64 grams	186 mg 70%	246 mg 61%
Fetal cortex	portion of gland 87%	24.3%	12.7%
	actual mass 4.26 grams	59 mg 99%	36 mg 99%
			54.5%
			68 mg 89%
			45.5%
			56 mg 99%

[41] from which the ratio of definitive cortex with medulla and fetal cortex were calculated. Adrenals from three cases of anencephaly were treated in a similar fashion the results of which are shown in Table II where it can be seen that the definitive cortex in anencephaly has a simultaneous and significant degree of atrophy with the fetal cortex, albeit of lesser magnitude. The function of these zones is the subject of much speculation.

The fetal zone forms normally up to at least the fifth month of gestation [36, 42, 3] the time when growth rate for this zone slackens during the course of normal development but subsequently in the anencephalic, it involves almost completely by term. Figure 6 shows adrenals weighing 70 mg from a 'normal' fetus of five months' gestation as compared with adrenals weighing 63 mg from an anencephalic fetus of five months' gestation. The small adrenal of the anencephalic at term, therefore, represents atrophy and not agenesis. Figure 7 shows a microscopic section of the atrophic cortex with definitive zone present and fetal zone absent.

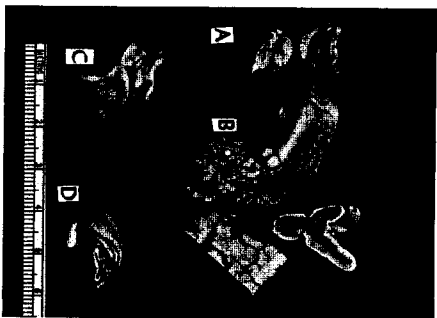


Figure 6. A, adrenal from normal fetus of five months' gestation; weight 0.70 grams. B, adrenals from normal term fetus; combined weight 0.63 grams. C, adrenal from premature anencephalic fetus of five months' gestation; weight 0.63 grams. D, adrenal from anencephalic fetus at term; weight 0.45 grams. (After Nichols with permission Amer. Med. Ass.)

Hormonal Relations

Absence of fetal zone in the anencephalic has been tacitly assumed the result of 'absence' (or deficiency) of anterior lobe pituitary tissue (ACTH). ANGRAVA [2] in 1928 demonstrated anterior lobe tissue by serial sectioning in all of 28 anencephalic fetuses, albeit, in some cases the amount was very small. He could not correlate the amount of pituitary with the degree of atrophy of the adrenal cortex.

The questions of why the fetal zone in the normal infant begins involution at birth, and why it begins involution after the 5th month of intrauterine life in anencephaly are enigmas. One school of thought summarized by CHESTER JONES [9] suggested that sudden withdrawal

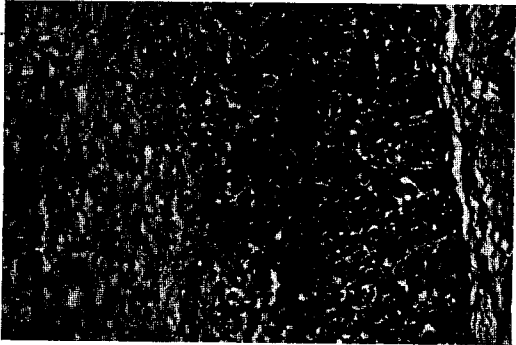


Figure 7. Section of adrenal cortex from atrophic adrenals from case of anencephaly in Figure 5. The entire cortex consists of deeply staining cells histologically identical with those of the definitive cortex of a normal newborn. The innerstrip adjacent to the medulla is devoid of fetal cortex and is composed of loose edematous mesenchyme. Hematoxylin and eosin, magnification 130 \times . (after Nicius *et al.*, with permission of the Endocrine Society).

of gonadotrophic hormone at birth, possibly, in part, from the placenta, may be the initiating factor for involution of normal fetal zone. This would not explain the normal growth of this zone until the fifth month and its subsequent atrophy prior to birth in cases of anencephaly. Constant histological defects have not been noted in placentas of anencephalic infants. Whether or not atrophy of the fetal zone in anencephaly is due to deficient ACTH is open to serious doubt. The adrenal cortex of the newborn reacts very sluggishly to exogenous

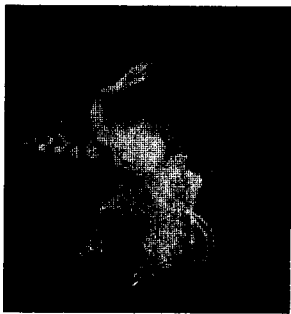


Figure 8. Radiograph of skull in a case of microphall at term illustrating small size of vault in comparison to facial bones. The pituitary sella contained a normal pituitary gland, yet the adrenals showed atrophy characteristic of anencephaly (after Javicus *et al.*, with permission of the Endocrine Society).

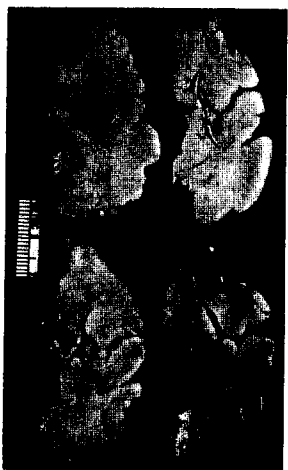


Figure 9. Coronal section of brain in a case of microphall at term showing incomplete development of gyri, rudimentary ventricular system, and absence of hypothalamus. The pituitary in this case was considered normal, yet the adrenal glands showed atrophy characteristic of anencephaly (after Javicus *et al.*, with permission of the Endocrine Society).

porine ACTH [27], as judged by urinary excretion of hormones, and injection of exogenous ACTH does not impede involution [29] of the fetal zone. Perhaps it might respond to injection of human ACTH.

This author [43] has found ACTH present, by the method of Neison and Home [40], in pituitary and/or sella tissue in all of five cases of anencephaly. The amount could not be determined quantitatively because the tissue by histological examination was composed in large and varying part of nonpituitary mesenchyme, and some tissue was necessarily utilized in the histological preparations. If the fetal zone is dependent on ACTH for its integrity and becomes atrophic in the anencephalic because of lack of ACTH, it would mean simultaneously that the definitive zone is less dependent on ACTH, because atrophy of the definitive zone is not as profound as atrophy of the fetal zone. Perhaps the plasma ACTH levels in anencephalics and normal infants will be compared and the answer forthcoming when bio-assay for ACTH becomes more sensitive. Although ACTH has not been determined in the placenta of anencephalics, there is no reason to doubt its presence, and therefore, availability as a stimulus if the fetal zone is susceptible.

There is ample evidence of at least two kinds of ACTH for the adult human adrenal gland, one a weight maintaining factor and the other a steroid releasing and/or forming factor. These two ACTH's are sometimes formed in tissue other than pituitary, e.g., lung tumors [44]. Atrophy of the fetal zone in anencephaly could be explained by either a) the absence of a 'fetal adrenal ACTH' from the cerebrum and midbrain which would act directly on the fetal zone (and definitive zone) in the normal fetus, or b) absence of a 'fetal adrenal corticotrophin releasing factor' which would stimulate the fetal pituitary to form a special 'fetal adrenal ACTH'. These postulated factors would not be needed prior to the 5th month of gestation, but would be required subsequently.

Many cases of microcephaly and hydrocephaly show varying degrees of atrophy of the fetal adrenal cortex usually paralleled with absence of CNS tissue and with varying amounts of pituitary tissue. Figure 8 shows the skull, and Figure 9 shows the brain in two cases of microcephaly where the corpus callosum and hypothalamus were absent [24]. The cerebral tissue was greatly reduced in amount yet the pituitary grossly and histologically was normal, but the fetal zones were absent. Instances such as these, a diminished amount of cer-



Figure 10. This represents the brain in a case of congenital hydrocephaly due to atresia of the aqueduct. The cerebral hemispheres and hypothalamus are, for the most part, reduced to a thin walled sac. Two small islands of cerebral tissue, a small fragment of cerebellum and a deformed medulla are present. The flattened isolated pituitary and atrophic adrenals did not react to metopirone (SU 4885). The infant lived 9 days.

bral tissue is present but the hypophysial portal system is absent. Figure 10 shows the 'brain' from a case of hydrocephalus in which the infant lived nine days. The cerebral hemispheres are reduced to a sac with a thickness of 0.5 mm; the basal ganglion, choroid plexus, and midline structures are markedly atrophic due to massive internal hydrocephalus from atresia of aqueduct of Sylvius. The isolated anterior lobe of pituitary is flattened and reduced in mass, while the adrenals show atrophy characteristic of anencephaly. Posterior lobe tissue is not present. Plasma 17-OHCS (Porter-Silber chromogen) determinations were done in this infant on each of five days, i.e., two days prior to administration of SU 4885 (Metopirone) in four doses of 100 mg each by gavage at six hour intervals and for two additional days at which time the infant died. Urine collection was unreliable. The plasma values were 1.5, 1.7, 1.8, 1.8, and 1.7 micrograms per 100 ml on the five days. This lack of response could be due to either a) refractory or inadequate adrenal, b) refractory or inadequate pituitary, or c) both.

Function of Fetal Zone

Function of the fetal zone formerly was entirely speculative, however, recently some clues have been obtained. It was held, by many, that androgenic hormones were formed in this zone, because the newborn infant excretes large quantities of 17-ketosteroids which decline parallel with involution of the fetal cortex. Considerable evidence has accumulated indicating that this zone does contain C_{19} steroids and can, *in vitro*, perform many biochemical steps necessary for production of androgens [4, 6, 50]. DICKSON *et al.* [14] report an anencephalic with high levels of plasma 17-ketosteroids 12 hours after birth. NICHOLS *et al.* [45] reported that plasma of 5 newborn anencephalic infants had normal amounts and normal maternal-fetus gradient of 17-OHCS. The 17-ketosteroids in three of these infants were in the normal range and in two of these cases plasma dehydroiso-androstosterone sulfate was very low, a finding also noted by SIMASK *et al.* [49]. This suggests that physiological function of the fetal zone does not necessarily reflect its pharmacologic capacity.

The most interesting work recently has come from the laboratories of FRANSDEN and SYRASKAWAN [18, 20] who report patients pregnant with an anencephalic fetus do not excrete the high estrogen levels characteristic of pregnancy, but instead excrete a low level characteristic of the non-pregnant woman. This has been confirmed by CORTIS [13] by injecting into spayed immature mice a) adrenal cortex, b) placenta and c) adnexal and placenta from premature normal fetuses obtained at therapeutic abortions, it was found that neither adrenal cortex nor placenta alone caused estrogen effect, but when adrenal and placenta were injected together, the mouse showed estrogen effect. From this they concluded the fetal adrenal cortex produces a precursor steroid from which the placenta forms the high level of estrogen characteristic of pregnancy. MACDONALD and SIRREY [31, 32] with radioactive material concluded that this precursor is dehydroiso-androstosterone. From the fact that the definitive zone also undergoes profound involution, in anencephaly it does not seem justified to conclude that this capacity to form estrogen precursor is limited to the fetal zone. It is to be noted that FRANSDEN and SYRASKAWAN injected 'adrenal cortex', presumably both definitive and fetal zones. They did not separate and inject a) definitive zone, b) fetal zone and c) both definitive and fetal zones nor have they injected adrenals from

cases of anencephaly formed mainly of definitive zone. The function of the fetal zone is, therefore, not yet settled.

Because the fetal zone of the human adrenal is often confused and/or compared to the 'X-zone' of the mouse adrenal, a few words about the latter is in order. This zone develops in the mouse adrenal about 21 days after birth and occupies a position between the zona reticularis and medulla. In the male it begins involution at about 45 days of age simultaneous with appearance of androgens from the testicle, and in the female it persists for about 250 days or onset of pregnancy, whichever comes first. During pregnancy in the mouse a small quantity of androgens is produced, as some are produced in aging ovary. The X-zone can be maintained indefinitely by castration or made to disappear at any time by injection of androgens and, therefore, obviously is quite different from the fetal zone of the human gland [10].

Other Glands

Gross and microscopic examinations of the other glands in anencephaly reveal no findings comparable in magnitude to atrophy of the adrenals and deficiency of the pituitary gland. Grossly the thyroid gland is normal and microscopically it appears, perhaps slightly, more mature than from a normal infant of corresponding age. Protein bound iodine determinations on maternal and cord blood in two cases of anencephaly reveal respectively the following maternal: fetal ratios, 9.0 : 10.8 and 11.2 : 10.6 micrograms per 100 ml. The author knows of no comparable data, but this suggests fetal thyroid function to be normal or hypertensive in cases of anencephaly. In two cases of anencephaly the maternal PBI was 8 and 13 micrograms per 100 ml and the thyroxine binding globulin 32 and 41 micrograms per 100 ml respectively. This is about twice the values of the non-pregnant woman and is the same level as found in the woman pregnant with a normal fetus and high estrogen levels. Because these women had low non-pregnant estrogen values the prevalent theory that PBI and thyroxine binding globulin are increased due to the accompanying high estrogens [15, 53] is open to question. Of course, normal appearance of the thyroid in anencephaly may be due to long acting thyroid stimulating hormone which in the adult, at least, does not arise from the pituitary. The pancreas and the parathyroid glands grossly and microscopically appear normal. The gonads, both male and female,

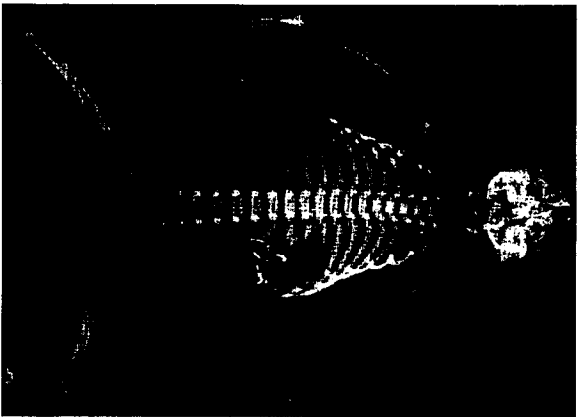


Figure 11. X ray of saccrocephalic infant, delivered from mother with polyhydramnios 5 hours after injection of barium sulphate into the amniotic sac. It can be seen that the infant has swallowed the barium, thereby eliminating "absence of swallowing" as cause of maternal polyhydramnios in this case. Coincidentally, there are healing fractures of the upper left humerus and upper right femur ("twisted child *in utero*") (WASSER and NICHOLS, unpublished).

appear grossly somewhat small and histologically slightly immature. Despite apparent low estrogen values, the vagina appears to be fully as cornified as in normal infants born of mothers with characteristic high estrogen levels. The author in his five cases has observed the pigmentation of the vulva and scrotum to be somewhat less than

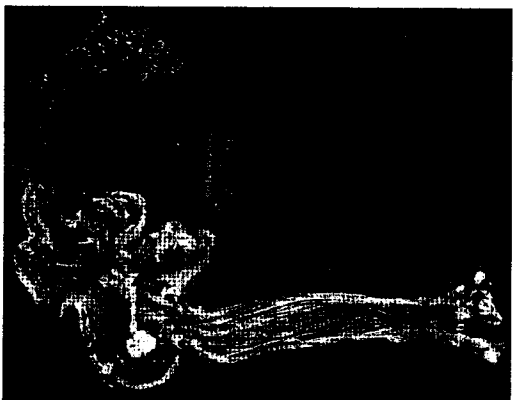


Figure 12. Esophagus, stomach, and duodenum of saccrocephalic infant in Figure 11 opened showing the megalo-esophagus and barium in the stomach (WASSER and NICHOLS, unpublished).

normocephalic infants, suggesting a low level of MSH. One characteristic finding is a large hyperplastic thymus. It is unlikely that this is due to atrophic adrenals, because plasma 17-OHCS and 17-ketosteroid values in anencephaly are not below those of the normal fetus. Despite the many defects present in the anencephalic the growth *in utero* is not impaired, except, perhaps a faster growth rate in the upper extremities [39]. The few rare cases which live a week or so die usually from sepsis, pneumonia, and atelectasis and not from endocrine causes.

Effect on the Mother

Anencephaly may have no effect on the mother. However, frequently polyhydramnios is present. In fact, when polyhydramnios is present, anencephaly or other malformation should always be suspected. Excess amniotic fluid is presumably due to a) excess formation from the exposed choroid plexus, b) absence of a swallowing reflex by the infant, c) impaired motility of the gut, d) increased urine formation by the kidney and e) decreased fluid absorption by the small crowded hypoplastic lungs. In the author's 29 cases, hydramnios was present in 18. Choroid plexus was found in only 5 of these cases. In 11 cases without polyhydramnios, choroid plexus was present in 4, and in all of these nine cases the choroid plexus was very small in amount. Figure 11 shows an X-ray of a newborn anencephalic with barium sulphate in the stomach. The mother had profound hydramnios and barium was injected into the amnion five hours before labor. The fact that the infant swallowed the barium indicates, in this case, that the hydramnios was not due to absence of swallowing despite megalocephalus (Fig. 12). This is contrary to the report of JERICOATE and SCOTT [25] who found that three of four anencephalics did not swallow radiopaque media injected into the amniotic cavity. At delivery the fourth case was a spurious diagnosis. In all the author's cases of anencephaly, meconium has been found in the small intestine irrespective of whether or not the mother had hydramnios. This suggests that the observed hypoplasia of the intrinsic plex [7, 35, 48] of the small intestine is not of great physiological importance.

BAINBRIDGE and MCKAY [5], in a histochemical study of two cases of anencephaly failed to find antidiuretic substance in the small amount of posterior lobe pituitary and neural tissue. They hold that this supports the idea that excess amniotic fluid may arise as a result of diuresis from nonreabsorbing kidneys. Urine outputs in cases of anencephaly which survive for a few days would be worth while on this point but such observations are not in the literature.

It seems that the low levels of estrogens in women pregnant with anencephalic fetuses do not have adverse effects on the course of the pregnancy although most cases of anencephaly have 1-2 weeks shorter gestation than the normal infant despite MALPAS' [33] report that anencephaly is one of the few absolute causes for post maturity. Twenty of the author's cases were 1-2 weeks premature, six were at term, and three were two weeks overdue. Assuming the incidence of

toxemia to be 5% and anencephaly to be 0.1% the incidence of toxemia associated with anencephaly should be 0.005%. The author does not know of a case. A few cases of hypopituitarism and hypoadrenocorticalism have been reported to benefit from pregnancy and the benefit attributed to fetal pituitary and/or adrenocortical hormones from the fetus crossing the placenta and entering the maternal circulation. It would be interesting to observe the effect of an anencephalic pregnancy when the mother has hypopituitarism or hypoadrenocorticalism. The author knows of no such case.

Finally a word may be said about intrauterine diagnosis which should always be made several months prior to labor. When a head is not felt on examination a) the patient is extremely obese, b) there is an anterior placenta covering the head, c) the fetal head has descended into the pelvis and can be felt from below, or d) the patient has an anencephalic, or microcephalic, fetus. The latter condition (d) justifies confirmation by X-ray so the patient may be informed and interested personnel alerted to conduct appropriate hormone studies. In the author's 29 cases, 15 were diagnosed prior to delivery, albeit, five of them very late pregnancy; 10 presented in labor without prior observation; and 4 were not detected by the attending physicians during prenatal care. Indeed, in 3 of the latter cases the position of the occiput had been recorded!!!

Summary

Anencephaly, a condition with absent forebrain and midbrain structures, occurs in newborn female infants with three to five times the frequency as in males. It has a unique geographic distribution, occurring in Ireland (0.6%) fifty times as frequently as in Lyons, France (0.012%). A genetic mechanism appears involved but cannot account for all cases; unknown diverse environmental factors undoubtedly are responsible for a large number of cases. The morphogenesis is uncertain, but several possible mechanisms exist. The condition may be produced by diverse agents in experimental animals.

A marked deficiency of anterior pituitary tissue is present but ACTH is present in sella tissue, albeit in small amounts. The fetal zone of the adrenal cortex develops normally, at least, until the fifth month of gestation, whereupon it involutes almost completely by time of birth. The fetal zone apparently forms a steroid precursor which the placenta converts into estrogenic hormones. This fetal zone, being

almost absent in cases of anencephaly and the definitive zone markedly hypoplastic causes the mother to have a low estrogen level characteristic of the non-pregnant woman. This low level of estrogens apparently has no adverse effects on the course of the pregnancy. The most likely cause for the atrophy of both fetal and definitive zones is absence of a neurohumor formed in structures of the fore and mid-brain which either stimulates directly the fetal adrenal or a neurohumor which stimulates the pituitary to form a special 'fetal adrenal ACTH'. Anencephaly can and should be diagnosed with precision prior to labor.

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