dymal cells of the cat described here bear a striking resemblance to cells found in various other CSF-containing compartments in and around the central nervous system[8,11-18,22]. Certain vacuoles of the 'pial free cells' of the dog subarachnoid space[14] contained quantities of HRP reaction product either almost filling the lumina or simply adhering to the inner surfaces of the vacuolar membranes when the protein was introduced into the CSF. This occurred in a similar fashion in the SE cells of the AP in the present study, and, in fact, the appearances of the cells in electron micrographs of the 2 studies are remarkably similar. In all of the investigations referred to above, it has been suggested that systems of macrophages or macrophage-like cells regularly occur in the various CSF-containing spaces.

Supraependymal cells consistently occur on the surface of the cat AP at the caudal end of the 4th ventricle surrounding the entrance to the central canal of the medulla oblongata[19]. These cells have now been shown to be capable of phagocytosis of a foreign protein and to display all the characteristics of macrophages found, for example, in the 4th ventricle and subarachnoid space of dogs[12,18]. It therefore seems reasonable to suggest that the SE cells of the AP of the cat are macrophages, and further, that they form part of an extensive system of macrophages in the CSF-containing compartments both within and around the central nervous system.

The origin of the cells seen in the present study and in the studies referred to above is still unknown. It has been suggested that they may arise from monocytes, and may enter the CSF through the choroid plexus[22]; they may arise from ependymal cells or microglia-like cells of the brain parenchyma[15]. Similarly, the function of such macrophages has not been well established. They may remove normal metabolic waste from the underlying surface[22]. They may also act as a first line of defence against foreign organisms that invade the ventricular system since it has been shown[24] that membrane-limited viral nucleocapsids are incorporated into SE macrophages after experimental intracerebral inoculation of mumps virus into hamsters. Further experimental studies of this latter type are, however, necessary in order to establish with certainty the functional significance of macrophages on the ventricular surfaces of the mammalian brain.

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X-irradiation of mice in early fetal period influences dose-dependently sex ratio of offspring until weaning

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Summary. Fractionated X-irradiation of mouse fetuses on gestation days 11-13 resulted in a significantly increased postnatal mortality of female litters. This occurred only at 3 × 110 rad, which was the threshold for the formation of typical neuroepithelial, rosette-like malformations.

X-irradiation in the early fetal period, which is the most sensitive period (between gestational days 10 and 13) in the mouse for distinct histological effects on the central nervous system (CNS), results in a variety of malformations[2,3]. These anomalies (e.g. porencephaly[4]) partially originate from extensive perinatal repair processes and are therefore only lethal in the suckling period. In a previous report[3], we quantified the CNS lesion pattern at term and decided to look for correlations between these morphological criteria and the incidence of stillbirths or postnatal deaths.

Materials and methods. X-irradiation of pregnant mice was performed on gestation days 11, 12 and 13, as reported previously (180 kV, 10 mA, 0.3 mm copper plate filter, focus target distance 40 cm; dose rate 1 rad/sec)[3,4]. Originally we used irradiation doses of 3 × 100, 3 × 120 and 3 × 140 rad, but in our search for the threshold dose for clear-cut malformations, so-called rosettes[3], we concentrated mainly on a dose of 3 × 110 rad. The dams were born at the time scheduled. The stillbirths were collected immediately, and postnatal deaths were collected 3 times a day. The percentage of wasted litters was thus very low. The sex of these dead animals was determined by abdominal inspection. Another 37 control dams and 55 dams irradiated with 3 × 110 rad on days 11-13 were sectioned on day 18 post conception (p.c.). The individual positions of the fetuses in utero were recorded, and these fetuses were weighed and consequently inspected for their gonadal sex. The placental weights were also determined.

Results. The number of dams used in the various groups and the subsequent sex ratios of the offspring at weaning are listed in table 1. In the low dose range between 3 × 100 and 3 × 110 rad, the sex ratio (♂ : ♀) abruptly increased, which was caused by a high mortality of the females. This was most extreme in group III 2 with a male : female index of 76:24 (=3.16). As this effect was rather surprising at first, we attempted to confirm it by repetition. Although in the subgroups of III there was rather a large variance in the sex ratio, the effect remained more or less constant in each experiment. In the case of the higher irradiation dose (3× 120 rad, group IV), the sex ratios were completely balanced again. The intrauterine sex ratios at term, the sex ratios of stillbirths, as well as of the early postnatal deaths, are listed in table 2. The fetal sex ratios were 1.09 for the controls and 1.12 in the irradiated animals; besides this we found no preference for either sex for a distinct intrauterine position. We also found that the weights of the irradiated fetuses were uniformly reduced to about 66% of the control weights, irrespective either of sex or intrauterine position. Compared with the control animals, however, the reduction of the placental weights after irradiation to about 75% was less pronounced. The sex ratios of the stillbirths were also balanced: 1.09 for the controls and 1.15 in the irradiated animals. The altered sex ratio at weaning resulted exclusively from an increased mortality of the females within the first 48 h; especially in the first 8 h after birth, female deaths were nearly twice as frequent as male deaths. After 48 h the mortality rates were completely balanced.

The litters were observed intensively within the first 48 h after term. The animals that died within this period showed a marked reduction of movement towards the dams and were therefore usually situated at the periphery of the litter nest. They appeared rather cyanotic and showed a lower body temperature than the others, even when the cage temperature was elevated. When they were brought into close contact with the mother, we hardly observed any tendency towards suckling. In fact, this reflex could not even be achieved by bringing these offspring in direct contact with the nipples.

Discussion. These results clearly showed a sex-specific effect of prenatal X-irradiation on postnatal litter viability, particularly within the first 2 days of life. The increased mortality of the females could not be explained by any significant weight differences at birth exceeding the sex-dependent differences normally observed. Although the gonads were markedly smaller than usual, as has already been shown in many previous studies[5], this would never explain a specific lethality of either sex. Moreover, as we irradiated prior to gonadal differentiation[6], disturbances of steroid hormone-dependent perinatal differentiation processes in the hypothalamus[7] did not seem possible; even then no lethal effects could be suggested. The only possible effect might have been a greater X-irradiation sensitivity of the female than of the male hypophysis. In preliminary histological studies, however, we have not found any sex-specific difference in their morphological appearance. The only effect we have been able to observe so far by histological methods was an increased frequency of telencephalic cortex destruction in female offspring. This observation also included a marked reduction of cortex diameters and increased frequency of rosettes in females. The quantification of this finding is presently in progress. Another very important finding seemed to be a constant and marked diminution of the epithalamic structures observed only in females after prenatal X-irradiation. We suggest that this latter abnormality was responsible for the pups' profound lack of suckling, swallowing and mobility. As these reflexes are exclusively odour-guided in newborn rodents[8], we assume that the pups have a deficiency of the olfactory system. Although a direct lesion effect of X-irradiation on the rhinencephalon is also possible[9], an injury to the olfactory system seems to be more likely in our opinion. This view is supported by the neuroanatomical description of the epithalamus as an important 'olfacto-somatic correlation center'[10], by the clinical observation of defects in swallowing after destruction of the lateral thalamic nuclei[11], and finally by reports on the 'pivotal role of the lateral habenula in funneling information from limbic and striatal forebrain to the limbic midbrain area'[12]. This would also explain the impaired temperature regulation of the newborn, as this function is exclusively regulated by the olfaction capacity in newborn rodents[13]. Other authors[14] even claim that there is a functionally important, directly acting regulation between the epithalamus and thyroid activity. This, again, would explain the dysfunction of temperature regulation.

The only problem which still remains unsolved is the clear prevalence of morphological and functional injury in females at the specific dose of 3× 110 rad, which represented the threshold between a merely mild reduction in brain weight on the one hand and severe CNS destruction by rosette formation on the other. Presumably in early fetal development sex-specific functions, other than hormonal ones, i.e. on the chromosome level, are sensitive to irradia-

Table 1. Weaning sex ratios of litters from controls and mice which were X-irradiated during the fetal period (11-13 days p.c.)

Experimental procedure	Numbers of dams	♂:♀	Sex ratio
I Controls			
1	45	54.6:45.4	1.20
2	42	52.4:47.6	1.10
II 3× 100 rad	45	57.2:42.8	1.33
III 3× 110 rad			
1	11	67.8:32.2	2.11
2	21	76.0:24.0	3.16
3	38	68.8:31.2	2.21
IV 3× 120 rad			
1	29	48.5:51.5	0.94
2	48	51.4:48.6	1.06

Table 2. Sex ratios in utero, of stillbirths and of postnatal deaths from controls and mice which were X-irradiated during the fetal period (11-13 days p.c.)

	Sex ratio of controls ♂:♀	Sex ratio of irradiated dams (3× 110 rad) ♂:♀				
a) in utero	52.2:47.8 = 1.09	53.0:47.0 = 1.12				
b) of stillbirths	52.1:47.9 = 1.09	53.6:46,4 = 1.15				
c) of postnatal deaths	Till 48 h 50.8:49.2 = 1.03	Till 8 h 36.1:63.9 =0.56	24 h 41.7:58.3 =0.71	48 h 40.0:60.0 =0.66	1 week 51.1:48.9 = 1.04	2 weeks 52.0:48.0 = 1.08

tion in a nonlinear dose-response relationship[15]. At a higher dose, therefore, the sex ratios are balanced again, presumably due to the increased destruction.

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Follicles development in the foetal human ovary

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Summary. In the foetal human ovary, diameters of oocyte and follicle, as well as those of oocyte and nucleus, are found to be positively and linearly correlated with each other. Follicle diameter and number of granulosa cells also show a positive and linear relationship. Finally, in all ovaries examined, from 5 months after conception onwards, small antral follicles were assessed.

In the present report, the quantitative patterns of oocyte and follicular growth are described in the human ovary during the intrauterine life from 5 months post-conception (p.c.) onwards. 5 foetal (21 weeks to 7 months p.c.) and 4 prematurely born specimens were obtained from the L'Aquila Provincial Hospital. The foetuses were derived from cases of spontaneous abortion. The interval between death and fixation of the tissues varies between 12 and 15 h. The standard of preservation of ovarian tissues was carefully checked during the initial examination of each specimen, and those which showed autolytic changes were discarded. In none of selected cases was there any maternal disease nor bad there been any pharmacological treatment.

The tissues fixed in Bouin's fluid were embedded in paraffin wax. Serial sections cut at 7 µm were stained with Harris haematoxylin and eosin. The diameters of the follicle, oocyte and oocyte nucleus were obtained using the method described by Mandl and Zuckerman[1] for the ovary of the adult rat. In order to establish the pattern of oocyte growth in relation to follicle growth, oocyte and follicle diameters were compared and were found to be positively and linearly correlated until the oocyte reached a mean diameter of 37 µm at a follicle diameter of 60 µm. Thereafter, the oocyte growth versus follicle growth varies less rapidly (figure 1). In this connexion it is worth noting the similarity between regression equation here calculated for foetal ovary ($y = 0.53\ x + 7.56$) and corresponding equation obtained by Lintern-Moore et al.[2] for infant ovary (phase A) ($y = 0.57\ x + 9.89$) and for adult ovary ($y = 0.55\ x + 9.32$).

Regression equation was also calculated for the growth of the nucleus in relation to that of follicle, in the foetal human ovary. Oocyte and its nucleus diameters were positively and linearly correlated with each other (figure 2). The relative regression equation here calculated for foetal ovary ($y = 1.46\ x + 6.77$) was quite different from that for infant ovary ($y = 3.20\ x - 43.7$)[2]: the oocyte growth versus nucleus growth foetal ovary would seem to go on less rapidly than in infant ovary.

Finally, the relationship between follicle diameter and the number of granulosa cells in the widest cross-section of the follicle was tested and was found to be linear (figure 3): the proliferation of granulosa cells appeared to determine the

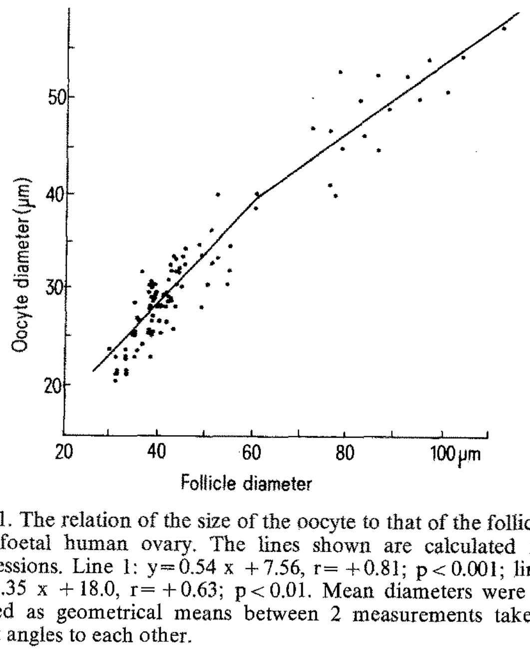

Fig. 1. The relation of the size of the oocyte to that of the follicle in the foetal human ovary. The lines shown are calculated from regressions. Line 1: $y = 0.54\ x + 7.56$, $r = +0.81$; $p < 0.001$; line 2: $y = 0.35\ x + 18.0$, $r = +0.63$; $p < 0.01$. Mean diameters were estimated as geometrical means between 2 measurements taken at right angles to each other.