Results. The resorption rate of litters exposed to 5-iododeoxyuridine in utero is shown in Table I. Over the dose range employed and throughout the developmental periods studied, both 500 mg/kg and 300 mg/kg were highly embryolethal. Only with the lowest dose (100 mg/kg) did intrauterine death approach previously reported control levels[7] and only treatment on day 7 resulted in a significant ($P < 0.005$) increase above these levels. The malformation rate in surviving fetuses is shown in Table II. Three major malformations: exencephaly, polydactyly and cleft palate are produced in sequence. In addition, omphalocele is produced by 300 mg/kg on day 8 (4%), syndactyly by 500 mg/kg on day 9 (3%) and ectrodactyly by 300 mg/kg on day 10 (18%).

Discussion. This study indicates that iododeoxyuridine is a 'classical' teratogen in many respects. First, one can define an embryolethal dose (500 mg/kg), a teratogenic dose (300 mg/kg) and a non-effective dose range (< 100 mg/kg). This is consistent with existing concepts[10,11] but is at variance with previously reported results with 5-bromodeoxyuridine in this strain of mice[7]. Second, the pattern of malformations produced follows a distinct stage-specifity and is qualitatively similar to those malformations observed after transplacental exposure to BUdR[7]. The findings reported here would suggest, therefore, that IUdR is a more potent embryotoxic compound but that it may produce congenital defects by a mechanism similar to its structural analog, BUdR. The difference in toxicity between these two compounds was unexpected but might be related to the vehicle employed (carboxymethylcellulose vs. distilled water), to different transport and incorporation kinetics, or to differences in maternal metabolism. In view of our previous studies which indicated that BUdR is incorporated into the DNA of the embryo on day 10 (stage 18) of gestation[7] coupled with the many studies which demonstrate that IUdR is incorporated into the DNA of susceptible tissues[12,13] leads us to propose that this latter compound is acting as a thymidine analog, and as such may be producing its biological effect by being incorporated into DNA. All of these factors: maternal metabolism, placental transport and incorporation into the DNA of the embryo are presently being evaluated by our laboratory and the final results will be the subject of a future communication[14].

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The Finding of Viral Particles in Spontaneous Mammary Adenocarcinoma in Rats

There are descriptions of the presence of viral particles in mammary carcinomas in the rat, experimentally induced with dimethyl-benzo-anthracene, with methyl-cholanthrene etc.[1]. These observations refer both to primary tumours and to transplantable tumours. Similar findings have been indicated in a mammary carcinoma of the rat obtained by radiation[2], and in cell cultures obtained from 2 mammary carcinomas of the rat induced with chemical means[3]. On the other hand, there have been no reports of viral particles in spontaneous mammary tumours of the same species[1].

We therefore considered it to be of interest to describe a case of spontaneous mammary neoplasia in this species, diagnosed histologically as adenocarcinoma, found in a uniparous 5 month-old female Sprague Dawley rat. The animal was one of a disease-free breed. Its appearance having been noted, the neoplasia tended to grow gradually, eventually reaching, after 7 months, the form and volume of a tangerine. In this period, fragments of tissue were removed, fixed both in osmic acid and in glutaric aldehyde and osmic acid and embedded in araldite-epon. In order to test the acellular transplant-ability of the neoplasia, the following tests were carried out, using both male and female subjects: 1. transplant of fragments of neoplastic tissue in the mammary region; 2. transplant of fragments of neoplastic tissue in the sub-cutis of the back; 3. transplant of neoplastic cells in the peritoneal region; 4. the peritoneal administration of acellular extracts of the neoplasia. Examination under the electron microscope showed type C viral particles, especially in the intercellular lacunae (Figure 1). In this region the particles in some cases appear clustered, but are more often free. They are seen to consist of an outer osmiophil ring and an inner one, the centre of which is rarely homogeneous.

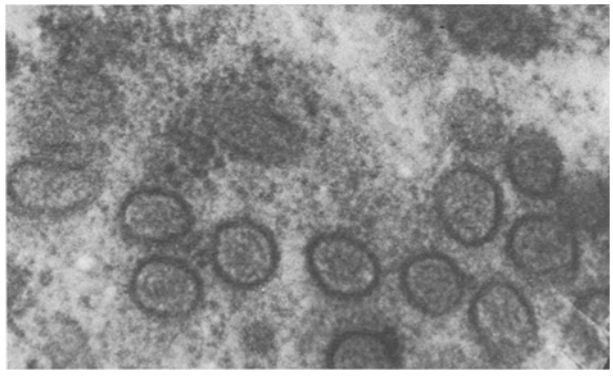

Fig. 1. Viral particles in the intercellular spaces. In some of them the inner membrane is fairly evident. Araldite-Epon; ×100,000.

Particles fundamentally of the same type have also been found in the cytoplasmatic region (Figures 2 and 3) especially in the vicinity of the edge of the cytoplasm. On some occasions particles connected together by an intermediate narrow part have been noted. The viral particles had a diameter of between 80 and 100 millimicrons.

Regarding the transmissibility, the only positive test was found to be that of a transplant of neoplastic tissue

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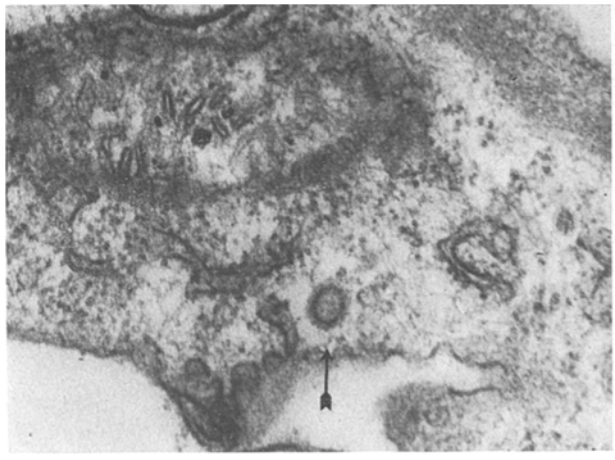

Fig. 2. Viral particles in the cytoplasmatic region. Araldite-Epon; ×50,000.

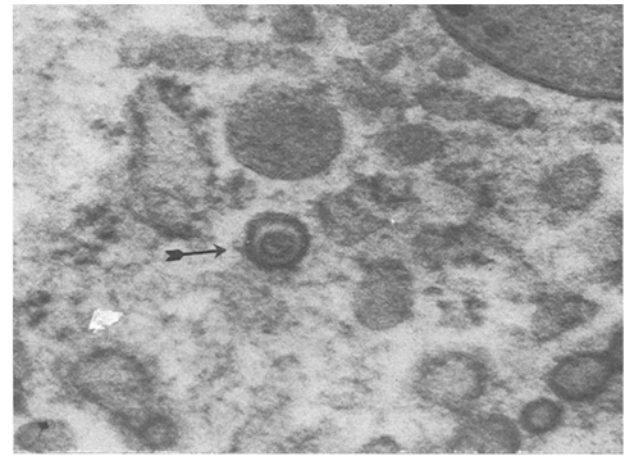

Fig. 3. Viral particles in the cytoplasmatic region. Araldite-Epon; ×100,000.

in the mammary area of female subjects, which regularly ensured, for 3 generations, the reproduction of the neoplasia. The other tests were found to be negative.

The case described above would seem to be the first one in which viral particles have been found in a spontaneous mammary tumour in the rat. However, this does not justify the proposal of any considerations regarding the etio-pathogenesis of the tumour in question. In fact, there is no possibility for correlating the evidential viral particles with the origin of the tumour, that arose spontaneously in the rat, in agreement, among other things, with what is know regarding cancer in the human species[4], even if in our case there is, in addition, the transplantability of the tumour.

Although there have been reports[5,3] of the possibility of inducing leukemias in the rat, with acellular extracts of mammary neoplasias of the same species, it would appear premature to draw any general conclusions, especially since these were cases of neoplasias induced with dimethylbenzo-anthracene. On the other hand, it would seem[1] that the virus isolatable from mammary carcinomas of the rat induced by radiation does not possess the same antigene constitution as the virus of murine leukemia.

As regards our results, we can merely say that, although the neoplasia is found to be transplantable, and inspite of the fact that viral particles have been found in it, it is not possible to conclude that it is of a viral nature. What has chiefly prevented us from doing this has been the absence of results following the inoculation of acellular extracts in numerous subjects.

Riassunto. Per la prima volta viene segnalato il reperto di particelle virali in adenocarcinoma mammario spontaneo del ratto.

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Effects of Placental Lesions on Foetal Growth in Rats

Normal growth of the foetus is dependent upon the functional integrity of the placenta and the maintenance of adequate foetomaternal exchange. Impaired uteroplacental circulation as well as placental insufficiency are commonly associated with foetal growth retardation in humans; thus predisposing to a high incidence of perinatal mortality and morbidity in such neonates, in spite of a full gestational period[1–7]. Experimentally, intrauterine growth retardation was obtained, following reduction of the utero-placental blood flow, in rats by Wigglesworth[8] and more recently in sheep by Creasy et al.[9]. Myers et al.[10] succeeded in inducing a condition of placental insufficiency and growth retardation of the foetal rhezus monkey by surgically interrupting the foetal blood vessels to the secondary placental disc. In the present study, an attempt was made to determine the effects of partial destruction of the placenta upon foetal growth in rats.

Materials and methods. 15 albino female virgin rats, 2 to 3 month-old, were mated. Successful mating was confirmed by sperms in the vaginal smear and this date was considered as day 1 of pregnancy. On day 17, the uterus was exposed through a midline abdominal incision, under general anaesthesia provided by intraperitoneal injection of Evipan-Natrium. The number and condition of conceptuses were recorded. Electrolytic lesions were made in alternating placentas of one uterine horn (experimental horn), while the remaining placentas of the same horn as well as all those of the contralateral horn (control horn) were kept intact. The lesions were made with stainless steel anodal electrodes using a direct current. In this system, the magnitude of the current remains constant and the extent of the lesion is mainly a function of the effective size of the electrode and the duration[11]. The bare end of the electrode measured 0.6 mm in diameter and varied between 3 and 5 mm in length