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Sensitivity of Newborn Mice to Carcinogenic Agents

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Studies involving the introduction of chemical carcinogens into newborn animals have yielded interesting results.

When 40 μg 7,12-dimethylbenz[*a*]anthracene in aqueous gelatine was injected subcutaneously into mice during the first 24 hr of post-natal life, a wide spectrum of tumours was induced, including lymphomas, pulmonary adenomas and adenocarcinomas, granulosa-cell tumours of the ovaries, adenomas of the renal cortex, skin papillomas and sebaceous adenomas, hepatomas, haemangiomas and haemangiosarcomas of various sites and papillomas of the forestomach epithelium (Roe *et al. Br. J. Cancer* 1961, **15,** 515). Telangiectasia of the forestomach was also observed. The induction of hepatomas, which is confined to the male sex, is a particularly striking example of a qualitative difference in susceptibility between the newborn and the adult (Roe & Walters, *Nature, Lond.* 1967, **214,** 299).

Different strains of mice differ in their susceptibility to neonatally administered dimethylbenzanthracene but most strains develop pulmonary tumours. The latter are usually multiple and particularly suitable for quantitative studies. There was a direct relationship between dose and average number of pulmonary tumours in BALB/c mice in response to dimethylbenzanthracene; 1·25 μg significantly increased their incidence in males and 2·5 μg did so in females (Walters, *Br. J. Cancer* 1966, **20,** 148).

Dimethylbenzanthracene (15 μg) administered subcutaneously in aqueous gelatine to a new-born mouse weighing approximately 1·5 g induced far more pulmonary tumours than the same dose given to a mouse weighing 6 or 18 g. It was also more effective than a 60-μg dose given to a 6-g mouse or a 180-μg dose given to a 18-g mouse. In the latter case, the differences were about two-fold in terms of the average number of tumours per survivor 40 wk after injection (Walters, *loc. cit.*). After the neonatal injection of dimethylbenzanthracene, feeding of a diet rich in protein (casein) led to a higher average yield of lung tumours (Walters & Roe, *Br. J. Cancer* 1964, **18,** 312).

When lymphomas of the stem-cell type are induced by the neonatal administration of dimethylbenzanthrene, there is a threshold time after which no more cases appear. This time varies in different strains (Roe *et al. loc. cit.*). In mice of the '101' strain there was some indication that new lung tumours induced by a neonatal injection of this compound ceased appearing after 60 wk of life (Walters & Roe, *ibid.* 1966, **20,** 161).

2-Naphthylhydroxylamine given neonatally proved more effective than 2-naphthylamine in the induction of pulmonary tumours (Walters *et al. ibid.* 1967, **21,** 367). The incidence was higher when aqueous gelatine was used as the solvent rather than arachis oil. 2-Acetylaminofluorene given daily in a dose of 100 μg/day on the first 5 days of life, increased the incidence of pulmonary tumours in mice, but a single dose was ineffective (Walters *et al. loc. cit.*). Ethyl methanesulphonate, 200 μg given daily on the first 5 days of life, gave rise to a high incidence of lung tumours (Walters *et al. loc. cit.*).

The neonatal subcutaneous injection of 45 μg dimethylbenzanthracene acted as an initiator of skin-tumour formation. This effect could be revealed by the subsequent repeated application of croton oil to the skin (Walters & Roe, *ibid.* 1967, **21,** 358). The neonatal injection of 3-methylcholanthrene in various doses had no consistent effect on the subsequent sensitivity of mice to applications of the same carcinogen to the skin. In a similar experiment, the induction of malignant skin tumours by benzo[*a*]pyrene applied to the skin was significantly delayed in mice treated with the same compound at birth (Grant *et al. ibid.* 1968, **22,** 346).

The administration of thalidomide to mice during pregnancy did not increase the incidence of neoplasia in the progeny (Roe *et al. ibid.* 1967, **21,** 331). In the doses given, no congenital abnormalities were seen either.

The injection of dimethylbenzanthracene into newborn hamsters resulted in the induction of numerous dermal melanocytomas, particularly of the eyelids. Other tumours induced were a squamous carcinoma of the penis, two malignant lymphomas and two haemangiomas—one of the ovary and one of the uterus (Walters *et al. ibid.* 1967, **21,** 184). In 40% of hooded rats of the August strain, the neonatal injection of urethane (8 doses of 1 mg/g body wt) induced melanocytomas of the iris (Roe *et al. Nature, Lond.* 1963, **199,** 1201). In rabbits, the neonatal injection of dimethylbenzanthracene resulted only in the induction of sarcomas at the site of injection in the subcutaneous tissues (Roe *et al. Br. J. Cancer* 1967, **21,** 815).

In general it has been concluded that a single injection of a test substance into a new-born mouse can not be regarded as a suitable screening test for carcinogenicity. In some cases the new-born animal seems to be especially sensitive to the carcinogenic effects of an agent, but for testing purposes, doses approaching the maximum tolerated level should be given repeatedly over a period, since a positive result is more likely to be achieved in this way. Aqueous gelatine was superior to arachis oil as a vehicle. A difference in the effects of a carcinogen on newborn and older animals may reflect a complete or relative absence of relevant enzymes in the former.

Experiments with Different Carcinogens in Pregnant Animals. Effect of Blastomogenic Substances on the Organism During the Period of Embryogenesis

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A review of the experimental data available in the literature has shown that present knowledge about the immediate and particularly the long-term effects of even well-known carcinogens on the progeny of mothers exposed to these agents in pregnancy is very frag-