CARCINOGENICITY OF A SINGLE ADMINISTRATION OF N-NITROSOMETHYLUREA: A COMPARISON BETWEEN NEWBORN AND 5-WEEK-OLD MICE AND RATS

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SUMMARY.—N-Nitrosomethylurea (NMUrea) was given as a single intraperitoneal injection either to newborn or to 5-week-old (C57BL × C3Hf)F_1 mice and Wistar rats. Newborn mice were more susceptible than 5-week-old mice to the development of lymphosarcomas, lung adenomas and hepatomas, whereas newborn rats were more susceptible than their weaned counterparts to the development of renal anaplastic tumours. Other tumours occurred with the same frequency in newborn and mature animals. Tumours of the forestomach in mice were more frequently found in animals treated at 5 weeks than in those treated at birth. Since NMUrea persists for only a very short time and breaks down spontaneously it seems that the paucity of enzymes related to immaturity in newborns is not a major factor in determining the different susceptibility of newborn animals to NMUrea carcinogenicity.

In several experimental systems, newborn or suckling animals were found to be more susceptible than mature animals to the effects of carcinogens. This difference is not fully explained; among other hypotheses, it has been suggested that the breakdown of chemical carcinogens is slower because of the enzymic deficiency of young animals. Powerful carcinogens such as 7,12-dimethylbenz-(*a*)anthracene, urethane and possibly N-nitrosodimethylamine persist unchanged for longer periods in newborn than in adult laboratory animals (Domsky *et al.*, 1963; Mirvish *et al.*, 1964; Terracini and Magee, 1964). N-nitrosomethylurea (NMUrea) was felt to be a suitable compound for testing this hypothesis, since in solution at pH around 7 it is unstable and is not likely to persist for more than a few hours (Druckrey *et al.*, 1967). NMUrea can produce tumours after a single administration (Druckrey *et al.*, 1964; Jänisch *et al.*, 1967; Kelly *et al.*, 1968; Leaver *et al.*, 1969); its carcinogenicity in newborn mice and rats has been previously investigated (Kelly *et al.*, 1968) but the available information does not permit comparison of newborn and more mature animals as regards susceptibility to tumour induction by NMUrea. Experiments on rats and different strains of mice have been undertaken in this laboratory to elucidate this point. The present work describes the effect of a single administration of NMUrea to newborn and 5-week-old (C57BL × C3Hf)F_1 mice and Wistar rats. Whereas as a whole newborns were more susceptible to tumour development than young adults, inconsistencies between different target organs have been found. In addition, several types of non-neoplastic lesions produced by NMUrea are described.

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MATERIAL AND METHODS

Hybrid (C57BL × C3Hf)F_1 (BC3fF_1) mice and Wistar rats from the colonies of this laboratory were used. Animals of both species were fed a commercial diet in pellets (Mangime Valleolona, Castellanza, Varese) and tap water *ad libitum*. Animals were treated within 24 hours after birth or at 35 days. Recrystallized NMUrea was obtained through the generosity of Mr. P. F. Swann, Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London. It was dissolved in saline immediately before use at a concentration of 0·1%. With the exception of one experiment, injections were given intraperitoneally at a standard dose of 50 μg./g., because preliminary experiments in newborn mice had demonstrated that 100 μg./g. produced a high early mortality. One additional experiment in rats was carried out with the purpose of directly exposing the thymus to the carcinogen: newborns from 4 litters received an intrathoracic injection of 50 or 100 μg. NMUrea (*i.e.* in the order of 8–16 μg./g.) as a 0·5% solution in saline. This was done under ether anaesthesia and through opening in the chest in the animals of one litter; rats of the other three litters received the solution of NMUrea as an injection through the thoracic wall.

Rats and mice were weaned at 3–4 weeks of age and separated according to sex. They were subsequently controlled daily and weighed at weekly or fortnightly intervals. The animals were allowed to die naturally or were killed with ether if obviously sick: all survivors were killed at 60–64 weeks of age.

A control group of BC3fF_1 mice was given only saline at birth. The pathology of a control group of 95 Wistar rats has already been reported (Della Porta *et al.*, 1968). During the performance of the present study the weight and the survival rate of the experimental rats were compared to that of an untreated group assembled at about the same time, which was over 2 years of age at the end of 1969.

Complete autopsies were performed on all animals, including opening of the spinal cord in rats. Histological sections were routinely prepared from the thymus, liver, kidneys and spleen, with the exception of a few animals highly decomposed. Endocrine organs were also examined in most rats. In addition, all organs grossly damaged were examined histologically. Specimens were fixed in Bouin and stained with haematoxylin-eosin: at least one coronary section from each kidney was routinely examined.

RESULTS

Survival rates are presented in Table I for both mice and rats receiving NMUrea i.p. and for control animals. Eleven of 95 mice treated at birth died before weaning compared with 3 of 34 controls. Early deaths did not occur in mice and rats treated at 5 weeks of age.

A consistent observation among animals treated at birth was in irreversible impairment of body growth. Fig. 1 and Table II show the pattern of body growth in mice and rats respectively. Growth depression was also observed, although to a much lesser extent, among mice treated at 5 weeks of age. All mice and rats treated at birth were smaller than the controls, regardless of whether they developed tumours or not.

Tables III and IV show the incidences of tumours observed in mice and rats respectively. Both tables indicate a high carcinogenic activity of NMUrea with the production of a broad spectrum of tumours. Only 7% of mice treated at

TABLE I.—*Survival Rates in BC3fF_1 Mice and Wistar Rats Treated with NMUrea 50 μg./g. i.p. once at < 24 hours or at 5 Weeks of Age*

Groups		Survivors at weeks of age						
		5	10	20	30	40	50	60
BC3fF_1 mice								
Controls	♀	11	11	11	11	11	11	11
	♂	20	20	20	20	20	20	20
NMUrea at birth	♀	45	45	25	20	19	18	17
	♂	39	38	22	16	14	14	11
NMUrea at 5 weeks	♀	45	45	40	32	24	20	18
	♂	35	35	34	29	25	24	21
Wistar rats								
Controls	♀	18	18	18	18	18	18	18
	♂	18	18	17	17	16	16	16
NMUrea at birth	♀	14	14	13	8	6	4	2
	♂	18	18	18	17	8	3	1
NMUrea at 5 weeks	♀	12	12	12	10	7	5	4
	♂	8	8	7	6	5	4	4

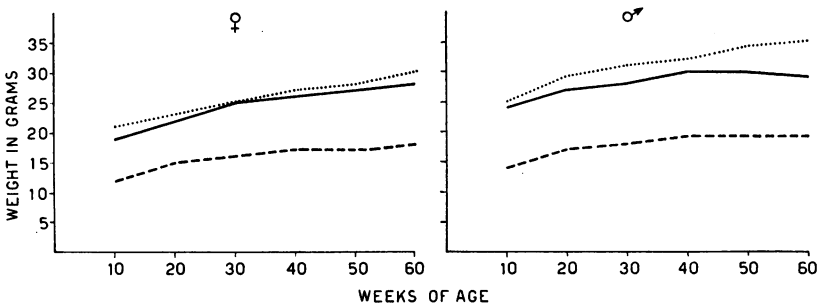


FIG. 1.—Body growth in BC3fF_1 mice given NMUrea 50 μg./g. as a single injection at 1 or 35 days of age.

..... Controls
— — — — — NMUrea at 1 day
———— NMUrea at 35 days

TABLE II.—*Weight (in grams) of Wistar Rats given NMUrea 50 μg./g. as a Single Injection at 1 or 35 Days of Age. Number of Rats in Brackets*

Treatment	Sex	Age in weeks		
		7	13	18
Controls	♀	140±2 (18)	227±17 (18)	233±2 (18)
	♂	170±6 (18)	305±11 (18)	350±10 (18)
NMUrea at 1 day	♀	64±2 (14)	116±19 (14)	129±3 (13)
	♂	77±5 (18)	163±11 (18)	194±12 (18)
NMUrea at 35 days	♀	130±3 (12)	204±4 (12)	232±4 (12)
	♂	159±2 (8)	302±6 (8)	357±10 (7)

birth and 21% of those treated at 5 weeks were tumour-free, compared to 97% among the controls. In rats treated either at 1 day or at 5 weeks, only 3 of 52 had no tumours at death. Multiple tumours in the same animal were commonly found. With the exception of mice with lymphosarcomas and rats with large

TABLE III.—*Carcinogenesis in BC3fF_1 Mice given a Single Intraperitoneal Injection of 50 μg./g. NMUrea i.p. at Birth or at 5 Weeks of Age and Killed at 60 Weeks**

Treatment		Mice dying with: Lymphosarcomas	%	Age†	Lung adenomas	%	Hepatomas	%	Renal adenomas	%	Forestomach tumours	%	Other tumours	Mice dying with no tumours	%
Controls	♀	0	—	—	0	—	0	—	0	—	0	—	0 —	11	100
	♂	0	—	—	0	—	1/20	5	0	—	0	—	0 —	19	95
NMUrea at birth	♀	23/45	53	17	16/19	84	1/17	6	3/18	16	4/17	24	12 (a)	4	9
	♂	23/39	58	18	12/15	80	10/12	84	3/15	20	0	—	2 (b)	2	5
NMUrea at 5 weeks	♀	21/45	46	29	10/35	28	0	—	0	—	12/18	66	8 (c)	7	13
	♂	11/35	31	29	10/26	40	0	—	2/21	9	8/22	36	3 (d)	10	29

* For each type of tumour results are reported as tumour bearing animals/survivors at the time of death of the first animal with that type of tumour.

† Average age at death in weeks.

(a) 1 s.c. sarcoma, 4 angiomas, 3 ovarian tumours, 1 papilloma of the vagina, 1 papilloma of the lip, 1 splenic reticulosarcoma, 1 squamous cell carcinoma of the rectum.

(b) 1 adenoma of the orbital glands, 1 cutaneous fibroma.

(c) 1 adnexal tumour of the vulva, 1 oesophageal carcinoma, 1 ovarian tumour, 3 adenomas of the orbital glands, 1 uterine sarcoma, 1 mammary tumour.

(d) 1 oesophageal carcinoma, 2 adenomas of the orbital glands.

TABLE IV.—*Carcinogenesis in Wistar Rats given a Single Intraperitoneal Injection of 50 μg./g. NMUrea i.p. at Birth or at 5 Weeks of Age and Killed at 60 Weeks**

Treatment		Rats dying with: Lympho-sarcomas	%	Renal anaplasti tumours	%	Age†	Renal adenomas	%	Forestomach tumours	%	Intestinal adenocarcinomas	%	Mammary tumours	%	Other tumours	Rats dying with no tumours
NMUrea at birth	♀	0	—	9/13	69	32	2/6	33	3/6	50	2/2	100	4/14	28	3 (a)	0 —
	♂	1/10	10	14/18	77	37	3/14	21	4/14	28	3/10	30	0	—	8 (b)	1 5
NMUrea at 5 weeks	♀	1/11	9	5/12	41	38	0	—	0	—	0	—	3/5	60	2 (c)	1 8
	♂	2/8	25	2/5	40	54	1/4	25	0	—	2/4	50	0	—	3 (d)	1 12

* For each type of tumour results are reported as tumour bearing animals/survivors at the time of death of the first animal with that type of tumour.

† Average age at death in weeks.

(a) 1 mediastinal myxosarcoma, 1 pituitary adenoma, 1 papilloma of the bladder.

(b) 1 angioma of the spleen, 2 keratoacanthomas of the skin, 1 rabdomyosarcoma of the tongue, 2 interstitial cell tumours of the testis, 1 adenoma of the adrenal medulla, 1 intracranial neurinoma.

(c) 1 pituitary adenoma, 1 mediastinal fibrosarcoma.

(d) 2 sebaceous adenomas of the skin, 1 splenic angioma.

anaplastic tumours of the kidneys, it was difficult to establish which tumour was causally related to death or sickness.

Lymphosarcomas.—Thymic lymphosarcomas and generalized lymphosarcomas with prominent involvement of the thymus were the tumours most commonly found in mice. There were great variations in the degree of involvement of organs other than the thymus. Among mice treated at birth, the incidence of lymphosarcomas in both sexes ranged between 50 and 60% with an average age at death of 17–18 weeks. The incidence of lymphosarcomas in mice treated at 5 weeks of age was 46% in females and 31% in males, with an average age at death of 29 weeks in both sexes.

Lymphosarcomas were found in one rat treated at birth and killed at 38 weeks of age, and in 3 rats observed at 16, 21 and 28 weeks of age among those treated at 5 weeks. With one exception in which the thymus was spared, they were generalized lymphosarcomas of probable thymic origin. No tumours of the lymphatic organs were seen among rats injected NMUrea intrathoracically. In 95 untreated rats of this strain, one generalized lymphosarcoma occurred in a rat dying at 17 weeks of age; another rat aged 113 weeks had hepatic and splenic lymphoma.

Tumours and non-neoplastic lesions of the kidneys.—Three mice of each sex among those treated at birth and 2 males treated at 5 weeks had cystic-papillary or trabecular, non-invasive renal adenomas. Only one of the tumours was greater than a few mm. in diameter and showed atypicalities, with no obvious invasion. No renal tumours were found in the control group. In addition, 27 mice of either sex treated at birth (including 4 with renal adenomas), 8 treated at 5 weeks of age and 2 control males showed single or multiple " hyperplastic tubules " in the renal cortex (Terracini *et al.*, 1966) (Fig. 2). Finally, among mice treated at birth, but not among those treated at 5 weeks or in the controls glomeruli with cell loss and fibrosis, occasionally with involvement of the Bowman's capsule, were seen (Fig. 3).

Renal tumours were the most commonly observed neoplasms among rats treated either at birth or at 5 weeks of age. They were bilateral in 11 rats treated at birth and in 1 treated at 5 weeks. Two different types of tumours were found, anaplastic or interstitial and tubular (Magee and Barnes, 1962; Riopelle and Jasmin, 1969). The incidence of renal tumours among survivors at 20 weeks of age was 74% in rats treated at birth and 37% in those treated at 5 weeks. Age at death of rats with renal anaplastic tumours was roughly similar in both groups. Only 1 anaplastic tumour was seen among 95 untreated rats from the same colony.

Six rats with renal tumours of tubular origin were observed throughout the present series. They were all less than 0·3 cm. in diameter and histologically appeared as solid or papillary adenomas; some contained areas of necrosis but no invasion or other signs of malignancy. In addition, 4 rats treated at birth had at least 1 hyperplastic tubule. Among 95 untreated animals, one renal adenoma and 2 adenocarcinomas were observed at an average age of more than 100 weeks.

Of the 32 animals of both sexes given NMUrea intrathoracically, 13 developed a total of 17 anaplastic and 2 tubular tumours.

Lung adenomas.—They occurred only in experimental mice surviving the period of high mortality due to lymphosarcoma. Animals treated at birth were more susceptible than those treated at 5 weeks. With the exception of 4 animals of either sex in the former group and 3 in the latter one, lung adenomas were found

in mice killed at the end of the experiment. Considering survivors at 40 weeks, incidences were 81% and 38% among those treated at 1 and 35 days respectively. Lung adenomas were usually multiple but only rarely did they largely replace the lung parenchyma.

Hepatomas.—This type of tumour was also seen only in mice. Data contained in Table III indicate a much higher susceptibility of males than females and a sharp loss of susceptibility at 5 weeks of age. Hepatomas were more than 0·8 cm. in diameter, on section they showed a trabecular pattern and compressed the surrounding parenchyma without invasion. No hyperplastic nodules or other lesions often associated with hepatocarcinogenesis were observed. Lung metastases were not seen.

Tumours of the forestomach.—The relation between age at treatment and subsequent tumour development appeared to be different in mice and rats. Tumour incidence was higher in mice treated at 5 weeks than in those treated at birth, whereas only rats treated when newborn developed this type of tumour. In mice, with the exception of a male treated at 5 weeks and dying with a squamous cell carcinoma at 54 weeks, all stomach tumours were papillomas found in animals killed at the end of the experiment. The 7 tumours of the forestomach in rats were papillomas observed in animals dying from other causes between the 33rd and 50th week of life. In addition, 1 papilloma of the forestomach was found among the rats given NMUrea intrathoracically. Four rats in the control group, aged more than 100 weeks, each had a papilloma of the forestomach.

Tumours of the intestine.—The only intestinal tumour in a mouse was a sarcoma in a male treated at birth. A total of 7 rats with intestinal adenocarcinomas were found: 1 tumour was located in the duodenum, 5 in the small intestine and 1 in the colon. An animal with intestinal adenocarcinoma also had a carcinoid of the caecum. Two borderline lesions, possibly non-invasive adenocarcinomas, were also seen, 1 of which was in a rat with an adenocarcinoma. Another adenocarcinoma of the intestine was found in 1 of the rats given NMUrea in the thorax. Two adenomatous polyps were found in the control group.

Mammary tumours.—The only mammary tumour in a mouse was found in a female treated at 5 weeks and dying at 42 weeks of age. In rats, 4 mammary tumours were found among females treated at birth (all were palpable before the 30th week of age) and 3 among those treated at 5 weeks of age (all of which were palpable after the 50th week of age). Two of the 17 females treated intrathoracically developed mammary tumours. Among the controls, 15 of 48 females developed mammary tumours, the earliest being palpable at the 86th week of age.

EXPLANATION OF PLATES

FIG. 2.—Female mouse given NMUrea at birth and killed at 30 weeks. Hyperplastic tubule in the kidney. H. & E. ×420.

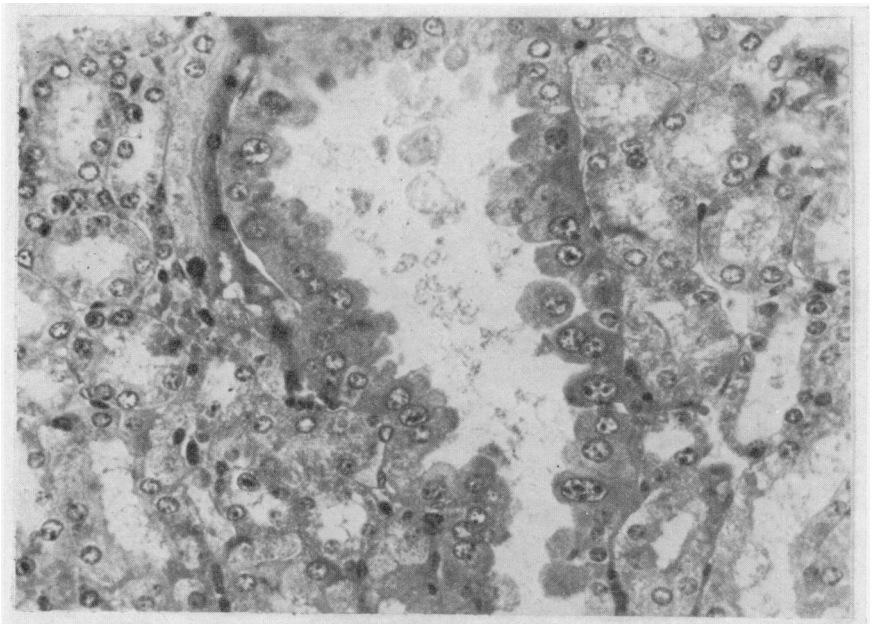
FIG. 3.—Female mouse given NMUrea at birth and killed at 46 weeks. Renal glomerulus showing thickening of Bowman's capsule and some increase of the mesangium. H. & E. ×510.

FIG. 4.—Male mouse given NMUrea at birth and killed at 22 weeks. Cutaneous cyst containing keratin. H. & E. ×90.

FIG. 5.—Same lesion as in Fig. 4. The cyst is lined by flat epithelial cells. H. & E. ×420.

FIG. 6.—Male rat given NMUrea at birth and killed at 44 weeks. Testicle showing atrophy of the germinal epithelium and hyperplasia of the interstitial cells. H. & E. ×70.

FIG. 7.—Male rat given NMUrea at birth and dying at 43 weeks. Intracranial neurinoma. H. & E. ×420.



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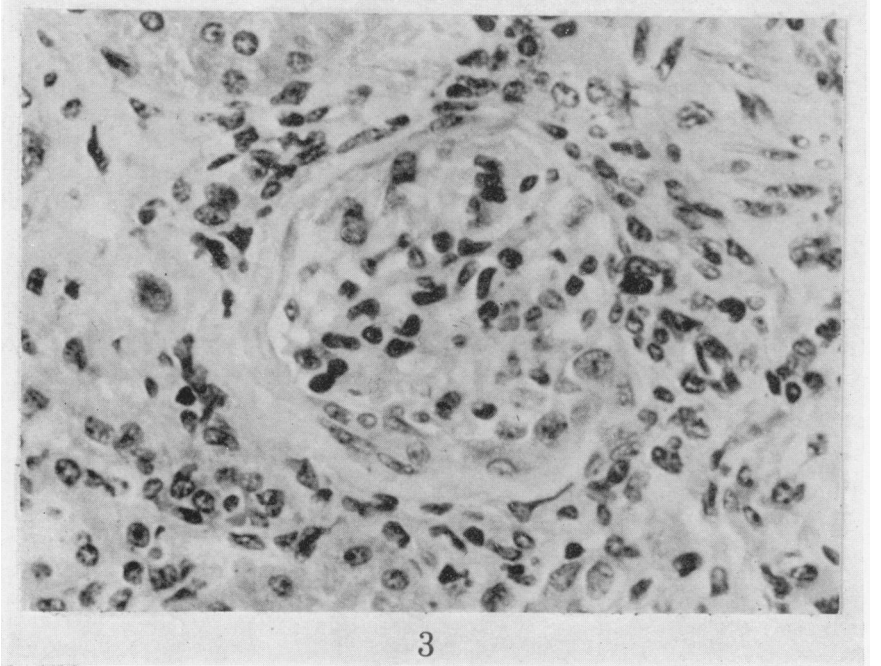

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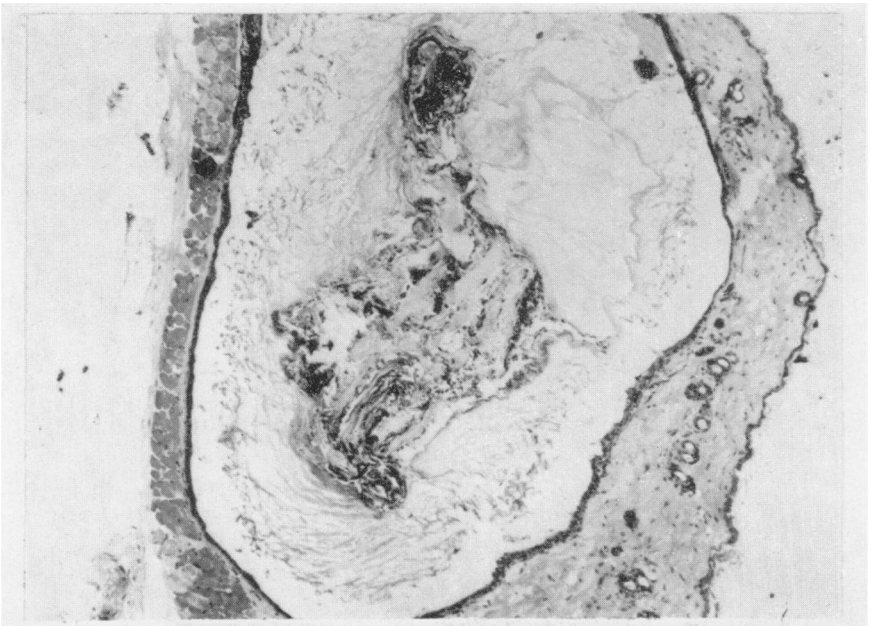

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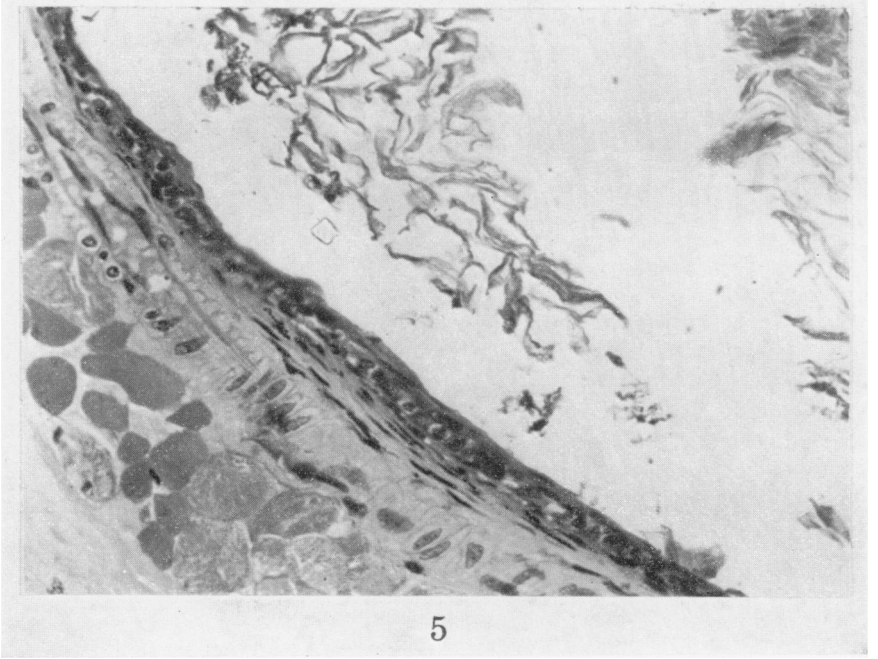

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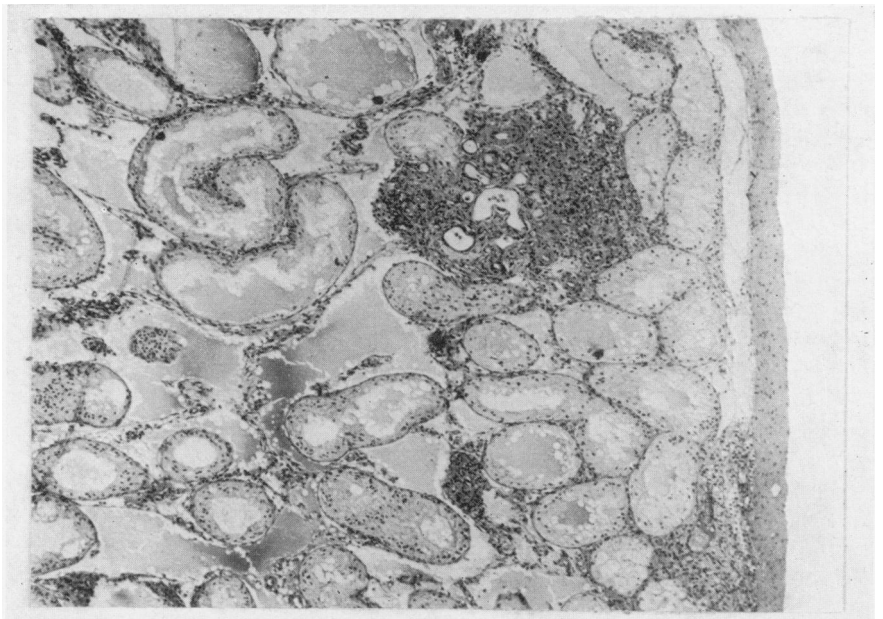

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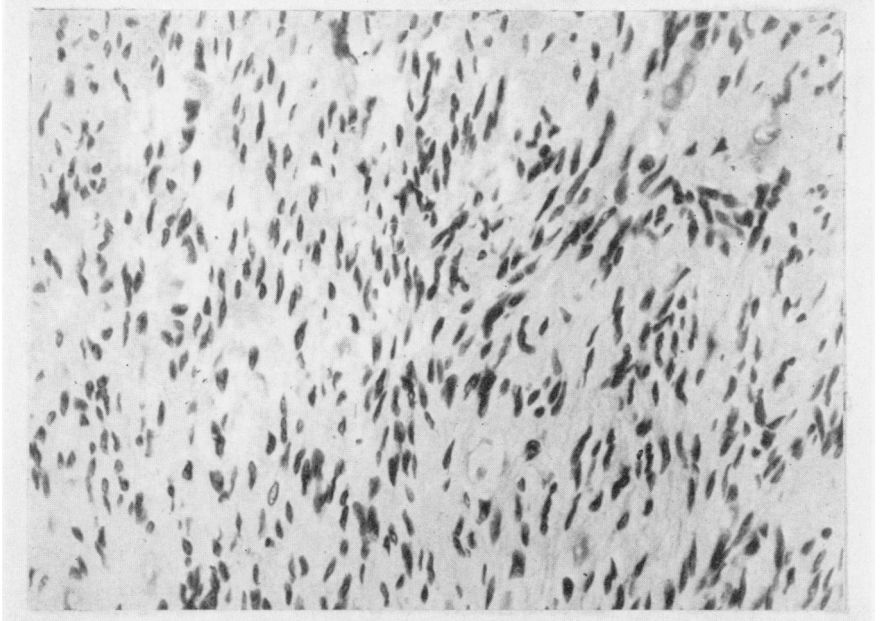

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Non-neoplastic lesions in mice.—The occurrence of hyperplastic tubules and hyaline glomeruli in the kidney has already been mentioned. In addition, at autopsy, in 29 mice treated at birth, but in none of those treated at 5 weeks or in the control group, there were multiple dark spots in the inner side of the skin; they were up to 0·2 cm. in diameter and histologically appeared as cysts containing keratin, lined by flat cells, associated with groups of melanocytes and occasionally with small foreign body lesions. The earliest change of this type was seen in a mouse dying at 15 weeks of age (Fig. 4 and 5). A common finding in female mice given NMUrea either at birth or at 5 weeks of age and killed at the end of the experiment was a dilation of the uterine horns associated with cystic hyperplasia of the endometrium.

Non-neoplastic lesions in rats.—Among rats treated at birth, the incisor teeth of several animals were irregular and very long and had to be cut several times. This was unlikely to be a major cause of stunted growth since there were no differences in body growth among animals with normal and abnormal teeth.

Another common finding in male rats treated with NMUrea at birth were small testes. On section, the germinal epithelium appeared atrophic (Fig. 6) and very few or no spermatozoa were present in the epididymis. A common finding in these testes was hyperplasia of the interstitial cells, which in 2 rats appeared as large areas classifiable as interstitial cell tumours (Table IV). Endometrial changes were seen only in a female treated at birth. Ovarian cysts up to 1 cm. in diameter were observed in 5 instances. No consistent changes were found in the pituitary, adrenals and thyroid.

DISCUSSION

Although a single administration of 50 μg./g. NMUrea proved to be highly carcinogenic to both species investigated, the type and location of tumours was different in mice and rats. This confirms a previous observation on the effects of NMUrea in newborn animals (Kelly *et al.*, 1968) and at present can be explained only on a speculative basis. Intrathoracic administration of carcinogens is known to enhance the occurrence of thymic lymphosarcomas in mice (Chieco-Bianchi *et al.*, 1965; Doell *et al.*, 1967) and this could be related to a higher amount of the carcinogen reaching the target organ; in the present study, however, rats given NMUrea intrathoracically failed to develop thymic lymphosarcomas.

In both mice and rats there were differences in tumour incidence between animals treated at birth and later in life. The present study confirms that lymphosarcomas, hepatomas and lung adenomas in mice as well as renal anaplastic tumours in rats are more easily induced in infant than in mature animals (Toth, 1968; Della Porta and Terracini, 1969). The earlier occurrence of mammary tumours in rats given NMUrea indicates a similar trend. However, in mice, stomach tumours occurred more frequently in animals treated at 5 weeks of age. The tumours at different sites indicated in the footnotes of Tables III and IV were probably related to the treatment and their incidence was not significantly different in animals treated at birth or later in life.

Since NMUrea breakdown is rapid and may not require an enzyme (Leaver *et al.*, 1969) it seems that factors other than the degree of maturation of enzyme production are related to the difference in susceptibility among newborns and young adults. Thus, the " organotropism " (Druckrey *et al.*, 1967) of NMUrea is different in mice and rats and is influenced by the age at treatment. Present knowledge is

insufficient to establish whether species- and age-related differences are the consequence of a different rate of absorption, a different distribution of the carcinogen or the different functional state of some organs in newborn animals.

NMUrea ranks among the most potent leukaemogenic chemicals in mice as single doses of 30 μg./g. or higher have produced incidences of lymphosarcomas of 40% or more in all strains so far investigated, *i.e.* XVII (Graffi and Hoffmann, 1966), outbred Swiss (Terracini and Stramignoni, 1967), inbred Swiss (Frei, 1969), NIH general purpose (Kelly *et al.*, 1968) and BC3fF_1 (in the present study). The order of magnitude of the effective doses and the percentage of mice developing lymphosarcomas are comparable to those observed following administration of 7,12-dimethylbenz(*a*)anthracene (Toth *et al.*, 1963); a single administration of urethane to newborn mice was equally effective only when given at a dose of 1 mg./g. and in Swiss mice (De Benedictis *et al.*, 1964) whereas in C3Hf, C3H, BC3F_1 and C57BL mice a longer exposure to urethane was required to produce lymphosarcomas (Della Porta *et al.*, 1967). In the present study, when 35-day-old mice were used, lymphosarcomas were induced, but their incidence was somewhat lower and the latent period (measured as age at death) was longer than in mice treated at birth. In the case of urethane in Swiss mice, susceptibility to the leukaemogenic effect of 1 mg./g. was found to decrease significantly between 1 and 40 days of age (De Benedictis *et al.*, 1964).

A different situation is created by lung tumours: the decreased ability of NMUrea to induce lung adenomas in mice aged 35 days contrasts with the observation that in experiments lasting at least 30 weeks, following single doses of DMBA, nitroquinoline oxide and urethane, the incidence of lung adenomas approached 100% in animals treated both at birth and later in life (Walters, 1966; Nishizuka *et al.*, 1964; De Benedictis *et al.*, 1962; Klein, 1966). On the contrary, the finding of a high incidence of hepatomas only in males given NMUrea at birth in an experiment lasting 60 weeks is similar to the observations following 20-methylcholanthrene or urethane (Klein, 1959; Chieco-Bianchi *et al.*, 1965; Klein, 1966).

Tumours of the forestomach were more numerous among mice given NMUrea when mature. This result contrasts with the finding that carcinogenesis in the forestomach by intragastric administration of 20-methylcholanthrene or urethane was similar in mice treated as infants or later in life (Klein, 1959, 1966).

In rats, the higher incidence of anaplastic renal tumours among animals treated at birth probably reflects a different susceptibility related to age. The observation of stomach tumours only in rats given NMUrea at birth might indicate a difference related to age at treatment, but the total number of tumours was small; in any case, the present results confirm that NMUrea can induce stomach tumours through a single parenteral administration (Druckrey *et al.*, 1964). The occurrence of some mammary tumours in female rats treated at birth or at 5 weeks of age confirms a single previous observation (Kelly *et al.*, 1968) and indicts the mammary tissue of the female rat as another target organ for the carcinogenic effect of NMUrea.

Among the tumours appearing at other sites in rats, and probably related to the treatment, only one was neurogenic and was an intracranial neurinoma (Table IV, Fig. 7). No tumours of this type were seen in the control rats. The sporadicity of tumours of nervous tissue in rats and mice following a single i.p. injection of NMUrea confirms a negative finding following a single intracranial administration (Kelly *et al.*, 1968) and contrasts with previous findings indicating

the nervous system as a major target for NMUrea. The latter results, however, were obtained in experiments in which the carcinogen was given either intravenously (Druckrey *et al.*, 1965; Fried and Fried, 1966; Jänisch *et al.*, 1967) or orally with a long exposure (Stroobandt and Brucher, 1968; Thomas and Bollmann, 1969).

A common finding in the present series of experiments was a marked impairment of body growth in mice and rats given NMUrea at birth. This effect was unrelated to tumour development, since it was found also in tumour-free animals; in addition, stunting growth was already obvious before weaning. Mice also showed some hyaline changes in renal glomeruli, as previously described (Terracini and Stramignoni, 1967). Other symptoms of homologous disease (Keast, 1968) such as diarrhoea and hair loss were absent. The effect upon body growth in animals treated at 5 weeks of age was much less marked or debatable.

The carcinogenicity of a single administration of NMUrea appears to be a valuable tool for the study of dose–response relationships in carcinogenesis in view of the effectiveness of the treatment and the rapid breakdown of the carcinogen. Studies along this line are in progress in this laboratory.

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