LYMPHOID RESPONSE IN 9, 10-DIMETHYL-1-2-BENZANTHRACENE (DMBA) INDUCED MAMMARY TUMOURS OF THE RAT. R. HEIMANN, J. C. HEUSON, W. PIESSENS, N. LEGNOS and G. GALLEZ (introduced by F. J. LEJEUNE). Department of Pathology and Laboratory of Clinical Investigation, Institut Jules-Bordet, Brussels.

The lymphoid response has been quantified in mammary tumours induced by a single gastric instillation of 20 mg of DMBA in female Sprague–Dawley rats at age 50 days.

The tumours have been classified histologically as poorly differentiated, atrophic and secreting (Archer and Orlando, *Cancer Res.*, 1968, **28**, 217).

The early appearing hyperplastic alveolar nodules considered by some as preneoplastic nodules showed no lymphoid response while true tumours of the same size induced a response. The response decreased markedly between 6 and 8 months after DMBA administration.

Continuously growing tumours and undifferentiated tumours usually showed a lymphoid response. Atrophic tumours generally showed no response and secreting tumours never showed any response.

When the tumour growth was stimulated by insulin, the lymphoid response was greater than in control tumours.

PROGESTINS AND MAMMARY CANCER INDUCTION. E. COEZY and G. RUDALI. Fondation Curie, Institut du Radium, Paris.

It seems that in the past little research has been devoted to the carcinogenic risk produced by progestins. An intensive programme has been developed in our laboratory in recent years to investigate this problem. It has been found that norethynodrel, ethynodiol diacetate and chlormadinone acetate do not accelerate or raise the frequencies of mammary tumours in intact C3H, RIII and (C3H × RIII)F1 females but norethynodrel and ethynodiol diacetate induce such tumours with a high frequency in castrated (C3H × RIII)F1 males. The same compounds have accelerated the appearance of the tumours in castrated (C3H × RIII)F1 females. Chlormadinone acetate does not produce tumours in castrated males and does not accelerate carcinogenesis in the spayed females.

MAMMARY TUMOUR AND HEPATOMA SUPPRESSION BY DIETARY RESTRICTION IN C3H A^{vy} MICE. C. ROWLATT, L. M. FRANKS and M. U. SHERIFF. Imperial Cancer Research Fund, London.

Dietary restriction has been shown to reduce the incidence of some tumours in mice (Tannenbaum and Silverstone, *Cancer, N.Y.*, 1957, **1**, 306).

C3H A^{vy} mice have the highest female mammary tumour incidence of any inbred mouse strain (Heston and Vlahakis, *J. natn. Cancer Inst.*, 1968, **40**, 1161) Hepatomata are common in the male. The strain carries the mammary tumour virus. In spite of this, in our experiments the incidence of these tumours in males and females was abolished completely and the lifespan extended by simple dietary restriction. In the female mammary gland development was inhibited. The lack of a target tissue could explain the absence of mammary tumours in the female but does not explain the reduction of liver tumours in either sex.

These results will be presented as an example of environmental factors influencing the development of tumours even in strongly susceptible hosts.

THE DOSE RESPONSE FOR THE INDUCTION OF KIDNEY TUMOURS IN THE RAT BY A SINGLE DOSE OF DIMETHYLNITROSAMINE. P. F. SWANN. Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London, and D. G. KAUFMAN. National Cancer Institute, Bethesda, Maryland, U.S.A.

Seven days on a protein deficient diet protects the rat against the lethal effect of a dose of dimethylnitrosamine so that a single dose can be given sufficient to induce kidney tumours in every animal (Swann and McLean, *Biochem. J.*, 1971, **124**, 283). Using this technique the dose response for the induction of kidney tumours is now being determined. This paper reports results obtained up to 80 weeks after injection of carcinogen. Different doses have produced between 10% and 97% incidence of tumours. Two types of tumours have been found. The predominant tumour is a renal mesenchymal tumour

(Hard and Butler, *Cancer Res.*, 1970, **30**, 2796), the other a renal adenocarcinoma. The dose response for total tumour incidence is a probit curve.

This research was supported by a grant from the C.R.C. and N.I.H. contract number 70-2199. We would like to thank Dr R. Madison for supervising the animal experiment.

THE DEVELOPMENT OF TUMOURS IN A FEMALE RAT AND HER OFFSPRING, FOLLOWING ADMINISTRATION OF DIETHYLNITROSAMINE TO THE MOTHER DURING NURSING.

R. SCHOENTAL and E. C. APPLEBY. Department of Pathology, The Royal Veterinary College, London.

Several workers have demonstrated acute and chronic effects in rats suckled by mothers treated during nursing, with toxic and carcinogenic substances such as pyrrolizidine alkaloids, cycasin, bracken etc., but no information was available with regard to the effects of diethylnitrosamine.

We administered this substance to 3 female rats nursing their young. One mother given 7 doses died after 9 months and had a kidney tumour; nasal and other tumours started to appear among her offspring from the 10th month of life.

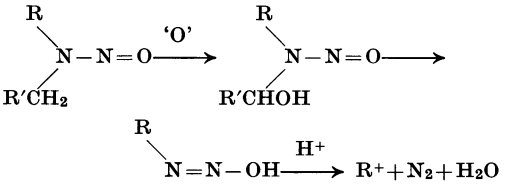
Recently, Mohr *et al.* (*Z. Krebsforsch.*, 1972, **78**, 72) reported nasal and respiratory tract tumours in golden hamsters, among the offspring and mothers treated with diethylnitrosamine during nursing.

Besides the parent nitrosamine, milk may contain in addition some of its biologically active metabolites. N-ethyl-N-nitrosoacetaldehyde has been suggested as one of the possible active intermediates in the carcinogenic action of diethylnitrosamine.

POTENTIAL ALKYLATING AGENTS FROM THE OXIDATION OF CARCINOGENIC CYCLIC N-NITROSAMINES.

B. C. CHALLIS and M. P. RAYMAN. Chemistry Department, Imperial College, London.

Carcinogenesis by some secondary N-nitrosamines may arise (Magee and Barnes, *Adv. Cancer Res.*, 1967, **10**, 163) from their alkylating action after metabolic oxidation of the α-carbon atom and subsequent decomposition to a diazo derivative (equation). The validity of this



hypothesis is apparently questioned by the properties of cyclic N-nitrosamines (*e.g.* N-nitrosopiperidine) that are potent carcinogens yet chemically inert.

We have shown, however, that N-nitrosopiperidine is oxidized by a model microsomal system (Udenfriend *et al.*, *J. Biol. Chem.*, 1954, **208**, 731) to N-nitroso-4-piperidone plus other products. This oxidation followed by ring cleavage is suggested as a mechanism whereby alkylating species could be generated.

INHIBITION OF METABOLISM AND TUMORIGENESIS OF 15,16-DIHYDRO-11-METHYL-CYCLOPENTA[A]PHENANTHREN-17-ONE BY 7,8-BENZFLAVONE.

M. M. COOMBS and C. W. VOSE. Imperial Cancer Research Fund, Lincoln's Inn Fields, London.

A number of cyclopenta[a]phenanthrenones have been tested for carcinogenic activity (Coombs and Croft, *Prog. exp. Tumor Res.*, 1969, **11**, 69).

The 11-methyl-17-ketone is a potent carcinogen for mouse skin. This ketone is metabolized by microsomal mixed function oxidases and binds covalently to DNA *in vitro* in the presence of rat liver microsomes.

7,8-Benzflavone, an inhibitor of the microsomal enzymes, inhibits covalent binding of the ketone to DNA at a 3 : 1 molar ratio of benzflavone compound. When 7,8-benzflavone is painted simultaneously with the ketone on mouse skin, suppression of the carcinogenic action of the ketone results. Thus metabolism of this ketone is required to cause *in vitro* binding to DNA and for its tumorigenic activity.

HYDROCARBON - DEOXYRIBONUCLEOSIDE PRODUCTS FORMED BY THE BINDING OF DERIVATIVES OF 7-METHYLBENZ[A]ANTHRACENE TO DNA.

W. M. BAIRD, A. DIPPLE, P. L. GROVER, P. SIMS and P. BROOKES. Chemical