WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

TRANSPLACENTAL CARCINOGENESIS

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IARC SCIENTIFIC PUBLICATIONS No. 4

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Proceedings of a Meeting held at the Medizinische Hochschule, Hannover, Federal Republic of Germany, 6-7 October 1971

ORGANIZING COMMITTEE AND EDITORS

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The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly as an independently financed organization within the framework of the World Health Organization. The headquarters of the Agency is at Lyon, France, and it has Research Centres in Iran, Kenya and Singapore.

The Agency conducts a programme of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment. Its field studies are supplemented by biological and chemical research carried out in the Agency's laboratories in Lyon and, through collaborative research agreements, in national research institutions in many countries. The Agency also conducts a programme for the education and training of personnel for cancer research.

The publications of the Agency are intended to contribute to the dissemination of authoritative information on different aspects of cancer research.

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FOREWORD

The International Agency for Research on Cancer is concerned in many different aspects of the study of environmental factors which may be responsible for causing cancer in man. Since many cancers make their appearance in later life, it is natural to consider that a long latent period is necessary after the exposure of an individual to a carcinogen before neoplastic development is observed. There is a tendency, therefore, to consider only the adverse effects of the environment on the adult individual.

Experimental studies have indicated the increased susceptibility of neonatal animals to the carcinogenic insult. The logical development of studying the effect on the rodent fetus of maternal exposure to a chemical carcinogen has made it clear that this pathway could well be operative in the human fetus. The discovery of the teratogenic effect of certain drugs administered to pregnant women has given considerable stimulus to the studies in this field, and the reports now appearing showing a carcinogenic effect on the daughters of women who had been exposed to stilboestrol during pregnancy indicate clearly that this approach is of great practical importance. The Agency was therefore very grateful when Professor U. Mohr agreed to organize a joint meeting at the Medizinische Hochschule in Hannover with the support of EUROTOX. He and his colleagues are to be congratulated on the excellent meeting that resulted. It is to be hoped that the publication of the proceedings will contribute to knowledge in this important field.

John HIGGINSON, M. D.
Director

International Agency
for Research on Cancer
Lyon, France

INTRODUCTION

At the time that this meeting, organized by the Agency in collaboration with the Medizinische Hochschule of Hannover, was being planned it could only have been suspected that there was an actual risk for man deriving from prenatal exposure to a chemical. The subsequent reports that appeared, showing by epidemiological studies that man was no exception to the risk of transplacental carcinogenesis, serve to underline the purpose of the meeting, which was convened to review the most recent experimental results in transplacental carcinogenesis and to assess their significance in relation to a possible carcinogenic risk for man. Research workers actively engaged in studying the effect of prenatal exposure to chemical carcinogens were brought together to review the current state of knowledge and to present their most recent findings.

We hope that the collection of proffered papers will not only provide an account of the present state of knowledge but also stimulate further research in this area.

We are especially grateful to Drs Miller, Rice and Montesano for their help in moderating and reporting the discussion. We acknowledge the support given to us by EUROTOX.

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PAPERS PRESENTED

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PAPERS PRESENTED

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Some General Considerations on the Problem of Transplacental Carcinogenesis

N. P. NAPALKOV [1]

"As one learns more about the natural history of [children's] tumours, an increasing number of fascinating research problems becomes apparent. Unless we are prepared to make the effort to tackle them, the future will remain as black as the present—and we shall have nobody to blame but ourselves."

Tumours in children, p. 12 (Marsden & Steward, 1968)

A group of experts discussed the problem of the potential carcinogenic hazards from drugs in man at the symposium held by the International Union against Cancer in 1965. The conclusions of that discussion were subsequently published by the Union and there is no need to repeat them here (Truhaut, 1967).

One of the symposium's recommendations, however, is worth particular mention. It pointed to the necessity of carrying out thorough studies of the possible risk arising from the carcinogenic effects of drugs which may be taken by women during pregnancy. The recommendation was made on the basis of only a few isolated experimental observations of so-called transplacental carcinogenesis reported up to that time. They were in line, to a certain degree, with Peller's conjecture (1960) that tumours in children may arise as a result of the transplacental effect of carcinogenic substances on the fetus. This inevitably led to the suggestion that a transplacental carcinogenic effect may be combined with a teratogenic one, in which case the immediate manifestations of the harmful effects of the substance on the embryo will become evident at a very early stage. Should this assumption prove correct, the results of short-term tests for teratogenicity could be used for evaluating the carcinogenic properties of chemicals. Solution of the problem of the immediate and long-term effects of carcinogenic agents on the organism during prenatal life is not only of theoretical importance in understanding the interrelations between teratogenesis and carcinogenesis. It is also closely connected with the search for aetiological factors and the development of measures for the prevention of tumours in children. It is an established fact that, during the last two or three decades, malignant tumours have become one of the main causes of mortality among children under 15 in most of the industrially-developed countries (Ariel & Pack, 1960; Marsden & Steward, 1968). According to the WHO figures published in 1967 and 1970, tumours were second only to accidents as a cause of mortality in children aged 5 to 14 years, and occupied fourth place in children aged 1 to 4 years. These figures for 1963–64 concerned the following five countries: Israel, Canada, United States of America, Federal Republic of Germany and Czechoslovakia. Malignant tumours also ranked second as a cause of children's deaths in England and Wales in 1964 (Marsden & Steward, 1968). Although tumours evidently tend to predominate among the causes of mortality among children, an absolute rise in tumour morbidity among children is less apparent. In any case, death rates from malignant tumours, which happen to be very similar to those for morbidity from this cause in children, ranged from 7.1 to 8.5 per 100 000 children under 14 in the above-mentioned 5 countries in 1964 (WHO, 1970). Other sources provide similar data.

This approximate equality of morbidity and mortality rates for malignant tumours in children is, unfortunately, determined by a number of factors, of which the absence of any distinct pre-cancerous changes with the consequent delay in diagnosis,

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which prevents clinical treatment, is one of the most important (Durnov, 1970). At present, prophylaxis by public heatlh measures is not feasible either, since the aetiology and pathogenesis of tumours in children have not yet been systematically studied. In fact, the problem was tackled only six or seven years ago, and the efforts of research workers, clinicians and epidemiologists in this field have not yet reached that stage of integration which Steward has so reasonably advocated (1966) and which can promise tangible success. However, the studies of Miller (1971) in the field of the epidemiology of tumours in children have already yielded some interesting data. For instance, an evaluation of child morbidity and mortality from malignant tumours in the USA in 1960–67 has shown the actual death rates for sibs to be much higher than those estimated for an average child population. A connection has been traced between the incidence of some forms of leukaemia and the occurrence of certain congenital or induced chromosomal abnormalities (Miller, 1966; Conen & Eckman, 1968; Miller, 1968b; Zuelger et al., 1968). Wilms's tumour, primary liver cancer, and gliomas and medulloblastomas have been found to occur frequently in combination with various malformations: Wilms's tumour with hemihypertrophy, aniridia, congenital defects of the heart and larger vessels, as well as with other anomalies (Lynch & Green, 1968; Miller, 1968a, 1968b); primary liver cancer with hemihypertrophy, haemangiomatosis and congenital atresia of the bile ducts (Fraumeni et al., 1968; Miller, 1968b); gliomas and medulloblastomas with phacomatosis (Miller, 1968b). Frequent combinations of certain other forms of congenital defects with tumours in children have also been reported. However, investigations have failed so far to reveal any connection between the neuroblastomas so frequently observed in children and congenital defects or hereditary diseases (Miller et al., 1968). Although all these clinical and epidemiological observations do not permit any far-reaching conclusions to be drawn concerning the causative relationships between hereditary diseases, teratogenesis and carcinogenesis in children, they provide oncopaediatricians with a means of determining which groups are at a higher possible risk from tumours.

The above observations lead to the logical assumption that, when a congenital defect in children is accompanied by a tumour, both these phenomena are either manifestations of successive stages of the same process or different consequences of the same cause. The first assumption appears to be improbable for cases in which congenital defect and neoplasm are localized in different areas, whereas the second seems to be of interest, particularly in the light of the experimental findings on teratogenesis and carcinogenesis caused by chemical agents. Moreover, clinico-epidemiological observations (Miller, 1968b) and mathematical evaluation (Emanuel et al., 1969) of the growth dynamics of such malignant neoplasms in children as Wilms's tumour, neuroblastoma, rhabdomyosarcoma and certain others have shown tumour onset to have been induced generally as early as embryogenesis.

The possibility of tumour development in adult humans as a result of exposure to carcinogenic substances has been repeatedly confirmed by the occurrence of the so-called occupational cancers. The occurrence of congenital defects in children as a result of the administration of certain chemical preparations to pregnant women was demonstrated by the Thalidomide catastrophe. Thus, we have a number of indirect indications which, nevertheless, seem to make it logical to assume that many tumours found in children may result from exposure to carcinogenic chemicals during embryogenesis. Direct clinico-epidemiological observations in this field are not yet available and one can hardly expect them to be collected in the near future.[1] Even the monograph by the oncopaediatrician Durnov (1971), in which particular emphasis is placed on methods of interviewing parents, contains no mention of the necessity of at least making an attempt to find out to what chemical agents the mother of the sick child might have been exposed during pregnancy. It is difficult to obtain the desired information from the interview with the mother, since our knowledge of exogenous carcinogenic substances and possible situations in which exposure may occur is still insufficient. But if one fails to intensify the efforts made to obtain such information, one can hardly expect the case history to become a source of qualitatively new data concerning the causes of tumour growth in children. Since the accumulation of such data is apparently complicated and involves many difficulties, the search for a solution to the problem may be assisted by extrapolating to humans the experimental results obtained from studies of the

[1] The data of Herbst et al. (1971) on the association between the administration of stilboestrol to mothers during pregnancy and the development of clear-cell vaginal carcinomas in their daughters were not available at the time this paper was prepared.

carcinogenic effects of certain substances during embryogenesis in various animals.

The fragmentary data on the immediate and, in particular, the long-term effects of the treatment of pregnant animals with certain carcinogenic substances, which were all that were available until recently, have become more comprehensive within the last two or three years. For instance, up to 1968, the possibility of inducing tumours in the progeny of animals treated during gestation had been demonstrated only in experiments involving urethane, dibenzanthracene, nitrosodiethyl- and nitrosodimethylamine, nitrosoethylurea and cycasin, as seen from the reviews by Di Paolo & Kotin (1966), and Napalkov & Alexandrov (1967, 1968). Diethylhydrazine, azo- and azoxyethane (Druckrey et al., 1968), aryldimethyltriazenes (Druckrey et al., 1969), dimethyl and diethyl sulphate (Druckrey et al., 1970), dimethylbenzanthracene (Tomatis & Goodall, 1969) and methylcholanthrene (Tomatis et al., 1970) have now been added to the list of substances capable of exerting a transplacental carcinogenic effect in experimental animals.

In the very early stages of research in the field of transplacental carcinogenesis, it became apparent that serious recommendations for the prevention of malignant tumours in children based on experimental observations could be developed only after a study of the relationships among the embryotoxic, teratogenic and carcinogenic effects of prenatal treatment with carcinogenic substances. Without knowledge of these relationships and a number of other features of transplacental carcinogenesis, it would be hard to say, at first, whether this experimental model was adequate from the point of view of the ultimate goal of the experiments, namely, the study of pathogenesis and the feasibility of cancer prevention in children.

For this purpose, our laboratory has since 1965 been systematically studying the primary response of the embryo (embryotoxic and teratogenic effects) and the long-term (blastomogenic) effect of certain nitroso compounds on the organism at the embryonic period of its development.

In the experiments on rats, we have studied the embryotoxic and teratogenic properties of the following highly carcinogenic nitroso compounds: nitrosodimethylamine and its diethyl, dipropyl and dibutyl homologues (NDMA, NDEA, NDPA and NDBA), nitrosomethylaniline and nitrosoethylaniline (NMA and NEA), nitrosomethyl-, nitrosoethyl-, nitrosopropyl- and nitrosodimethylurea (NMU, NEU, NPU and NDMU) and nitrosomethylurethane (NMUt). Nearly 1000 pregnant rats have been used in these experiments and changes in about 6000 fetuses have been followed.

As the results of these experiments have shown, symmetrical dialkylnitrosamines applied in different doses and administered for various lengths of time, by different routes and at different stages of embryogenesis, do not produce malformations in rats, but exert an embryotoxic effect only (Alexandrov, 1967). The effect proved non-specific and the mortality of fetuses was relatively high (about 40%) during the 1st and 2nd weeks of pregnancy but showed only a slight rise compared with controls after administration of NDMA in the last third of embryogenesis only, when administration of the same substance induces renal adenosarcomas in the offspring too (Fig. 1). It should be noted that these tumours were

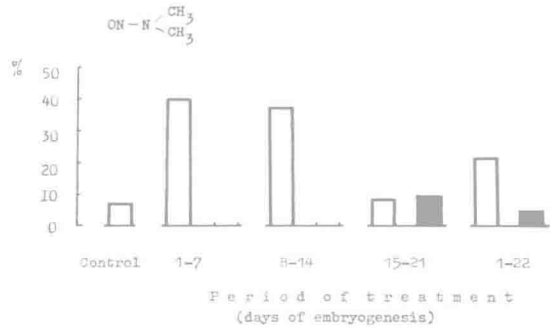

Fig. 1. Effect of administration of NDMA in rats at different stages of embryogenesis.

Embryotoxic effect (non-specific)

Teratogenic effect

Carcinogenic effect (kidney tumours)

The dosage of NDMA was 1 mg/kg per day during the 7-day periods and 0.5 mg/kg per day during the 22-day period.

not frequent and were found mostly in old rats (Alexandrov, 1968). The hypothesis of an indirect mechanism of symmetrical dialkylnitrosamine action due to formation of an alkylating metabolite produced by enzymatic demethylation of the original compound has been put forward by Druckrey et al. (1967). The absence of a teratogenic effect in our experiments may thus be probably accounted for by the failure of the activation of the original compounds to occur at teratogenesis-sensitive stages (organogenesis) because of the immaturity of the relevant

embryonic enzymatic systems. Meanwhile, the alkylating metabolite formed in the mother's organism fails to reach the embryo, since it is very reactive and is used up at the site of formation. The above conjecture, however, cannot provide a satisfactory explanation for the observations of the carcinogenic effect of NDMA when administered at later stages of embryogenesis. Moreover, the data of Lijinsky & Ross (1969) suggest that *in vivo* alkylation of nucleic acids by *N*-nitroso compounds may have nothing to do with their carcinogenic effect. This conclusion agrees with our findings (Napalkov & Alexandrov, 1968; Alexandrov, 1968), which showed that nitrosomethyl- and nitrosoethylaniline exert both an embryotoxic and a teratogenic effect on rat embryos. It was suggested, at the same time, that the production of malformations by aromatic *N*-nitroso compounds may depend on their ability to take part in the nitrosation reaction under certain physiological conditions. Finally, the mutagenic action of *N*-nitroso compounds was found to take place directly, and was not the result of diazomethane formation (Rappoport, 1969).

Nitrosoalkylureas were shown to have a strong embryotoxic and teratogenic effect, particularly when administered during organogenesis (von Kreybig, 1965; Napalkov & Alexandrov, 1968). However, antenatal administration resulted not only in the occurrence of malformations but also of a fairly high incidence of various tumours in the progeny (Alexandrov, 1969). As shown in Fig. 2, the occurrence of each effect of NMU and its extent are closely related to the stage at which the embryo is treated. These observations of the stage dependence of the effect corroborated the results of our experiments with NDMA mentioned above and similar findings from the study of the transplacental effect of NEU (Ivankovic & Druckrey, 1968).

The embryotoxic effect of NMU was very high for treatment during the 1st week of prenatal life and was associated with reduction of the embryoblast. This, as well as atrophy of the allantois and placentation disorders, may account for the high mortality of the embryos when the substance was administered in smaller doses but during the whole period of embryogenesis (Fig. 2). The teratogenicity of NMU was manifested by the induction of hydro- and microcephaly in the fetuses, following treatment during the 2nd and 3rd weeks of gestation or during the whole of embryogenesis. The worst and most frequent malformations, however, arose after treatment at the stages of organogenesis (days 8 to 14 after conception). A long-term effect, namely, tumour formation in the offspring, was observed in the experiments involving NMU administration to females at all stages of pregnancy, the highest incidence of neoplasms being recorded for treatment during the last

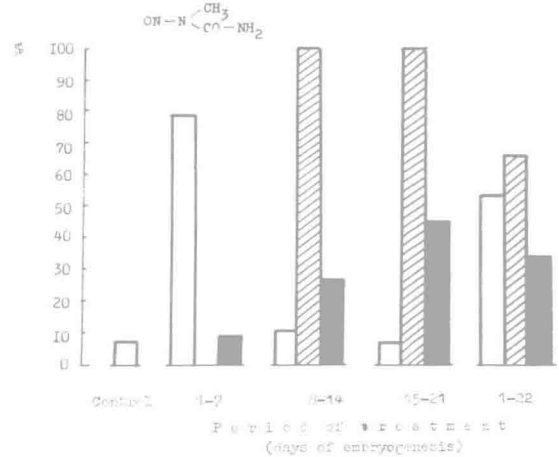

Fig. 2. Effect of administration of MNU in rats at different stages of embryogenesis.

Embryotoxic effect (reduction of the embryoblast, atrophy of the allantois)

Teratogenic effect (micro- and hydrocephaly)

Carcinogenic effect (tumours of the nervous system, kidneys, thymus, hypophysis, mammary gland and intestine)

The dosage of NMU was 3 mg/kg per day during the 7-day periods and 2 mg/kg per day during the 22-day period.

third of embryogenesis. Furthermore, treatment during the 1st and 2nd weeks of gestation resulted exclusively in mammary and pituitary tumour formation in the progeny, whereas administration of NMU during the last third or within the whole period of intrauterine development produced tumours, mainly in the nervous system and kidneys, in the survivors. It should be pointed out that instances of the joint occurrence of congenital malformations and tumours in the same organ, although very few, were found, for the first time, in the rats treated during the last third of pregnancy. Two rats which survived for more than a year had pronounced microcephaly and tumours of the brain hemispheres.

These findings were in good agreement with the results of subsequent experiments which attempted to determine the relationship between the teratogenic

and transplacental carcinogenic effect of NMU and its dose level (Fig. 3). A single injection of 5 mg/kg of NMU on the 21st day of gestation did not produce any apparent malformations and its effect was confined to the formation of tumours of the nervous system, kidneys and mammary gland in 27% of the animals.

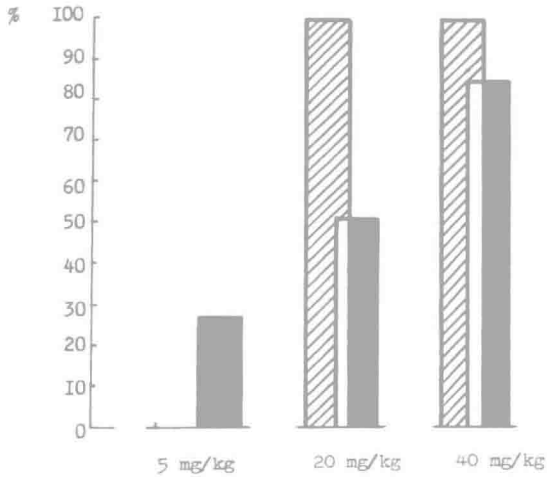

Fig. 3. Dependence of teratogenic and carcinogenic effects of NMU in rats on dose at the same stage of embryogenesis.

Teratogenic effect (hypoplasia of the medulla)

Carcinogenic effect (tumours of the nervous system, kidneys, thymus, hypophysis, mammary gland and intestine)

Treatment was given on day 21 of embryogenesis.

Similar tumours were found in 51% of the descendants of mothers treated with 20 mg/kg of NMU at the same stage of gestation; all animals were also found to have cerebellar malformations. A further increase in the dose up to 40 mg/kg of NMU invariably resulted in a higher tumour incidence in the offspring (85%) and was accompanied by more pronounced cerebellar hypoplasia in all the descendants. It is characteristic, however, that, although all the animals used in these experiments had congenital cerebellar defects, none of the rats was found to have a tumour at this site, although neoplasms occurred in other portions of the nervous system.

Thus it was shown that congenital defects may be induced in the final stages of embryogenesis, although by doses which are much larger than those required for a teratogenic effect at earlier stages, the sites of the malformations (cerebellar hypoplasia) and the tumours being different in this case too.

The next series of experiments undertaken in our laboratory was aimed at determining the stages of embryogenesis with the highest sensitivity to various types of transplacental effects of carcinogenic substances. In these experiments, the lives were followed of approximately 300 mother rats treated with single doses of NMU or NEU at different stages of gestation, and of about 1000 of their offspring. The results of these experiments appeared to agree with previous observations that the administration of a carcinogenic substance during the 1st, 2nd and 3rd weeks of embryogenesis results mainly in a strong embryotoxic effect, in a teratogenic effect, and in the induction of tumours in the offspring, respectively. In addition, two periods were found in which the embryo is highly sensitive to a lethal effect; these are the 3rd to 4th and 9th to 10th days of gestation in the case of NEU (Fig. 4). The highest teratogenic effect was shown to follow NEU treatment on the 10th day of embryogenesis. This increase manifested itself in the form of disorders of neurulation, i.e., abnormal formation and closure of the neural tube, which led to such malformations as hydrocephaly, exencephaly cerebral hernia, spina bifida, hare lip and anophthalmos. The carcinogenic activity of NEU after its transplacental administration was observed from the 11th day of embryogenesis onwards, the survivors having predominantly multiple tumours of the nervous system. It is hard to assess to what extent the development of these tumours is affected by the formation of the cerebral vesicles and the tissue differentiation of the nervous system occurring in the rat embryo exactly at this period of its prenatal life. One would have expected to find, in this case, congenital defects based on a disturbance in morphogenesis, and on inflammation at the fetal stage (Gul'kevich et al., 1971). The first tumours were found by the end of the 4th month of postnatal life. When the rats treated during the second half of embryogenesis were nearly 2 years old, almost all of them had neoplasms, mainly of the nervous system, but several had neoplasms of the kidneys, and single animals had tumours of the intestines and mammary gland, and leukaemias. A comparison of the transplacental carcinogenic action of the nitrosoureas on rats has shown their fetal response to NEU to be many times that for NMU.

Hence, it may be considered as established in the experiments on rats that the transplacental effect of

such substances as NMU or NEU, whose carcinogenic activity is not conditioned by metabolic enzymatic transformation, is determined by the stage of embryogenesis and, to a certain extent, by the dose of the compound concerned. Transplacentally induced tumours were of the same types, and arose at the same sites, as those produced by postnatal treatment with NMU, NEU and NDMA. To what extent are the parameters of transplacental carcinogenesis found for rats inherent to this particular species? Unlike its action in rats, when NEU is administered transplacentally in hamsters, it induces tumours which are not confined to the nervous system only (Ivankovic & Druckrey, 1968). However, in our laboratory, treatment of pregnant hamsters with 100 mg/kg of NEU 2 to 3 days prior to delivery resulted in the induction of tumours of the peripheral nervous system alone in 61% of the offspring. Treatment of pregnant mice with NEU in experiments by Rice (1969) showed that the adenomas of the lungs and tumours of the liver induced in this case are similar to those arising after postnatal administration of NEU. The highest transplacental carcinogenic effect in these experiments was recorded when animals were treated during the final days of pregnancy. Treatment with NMU and NEU in the similar experiments by Alexandrov & Likhachev in our laboratory, also induced only lung adenomas and adenocarcinomas in 71% and 74% of mice for NMU and NEU respectively. These are the scanty data available on the species peculiarities of the transplacental effect of two alkylnitrosoureas. Hence, for the time being, it can be said that, when animals of different species are subjected to the transplacental action of the same carcinogenic substance, the distribution of types of induced tumours and sites of occurrence is similar to that observed for postnatal treatment. This conclusion is also borne out by the results of the few comparisons so far feasible of the effects of the postnatal and prenatal treatment of different species with such substances as NDMA, NDEA, DMBA and methylcholanthrene. As in the case of the nitrosoureas, the characteristic tropism of the carcinogenic effects of each of these substances for a given species is the same for both prenatal and postnatal treatment. Similar results were recently obtained by Smetanin (1970) in experiments on C3HA mice

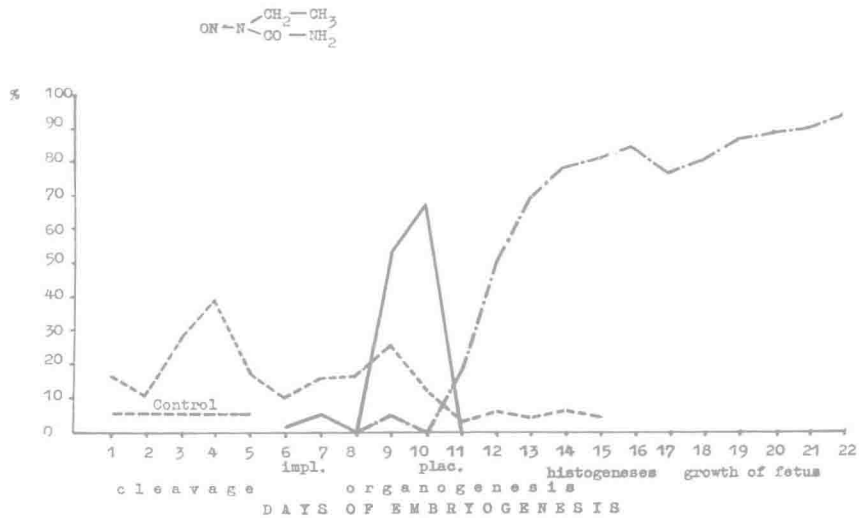

Fig. 4. Dependence of the transplacental effect of NEU on the stage of embryogenesis in rats.
– – – Embryotoxic effect (reduction of embryoblast, atrophy of allantois)
—— Teratogenic effect (hydro- and exencephaly, anophthalmos)
–·–· Carcinogenic effect (neurogenic tumours)
The dose of NEU was 20 mg/kg, i.v.

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