CC/NUMBER 17
APRIL 27, 1981

This Week's Citation Classic

Druckrey H, Preussmann R, Ivankovic S & Schmahl D. Organotropic carcinogenic effects of 65 different N-nitroso-compounds in BD-rats. *Z. Krebsforsch.* **69**:103-201, 1967. [Forschergruppe Praventivmed., Max-Planck-Inst. Immunol., Freiburg, Federal Republic of Germany]

Almost all tested N-nitroso-dialkylamtnes and -acylalkylamides revealed striking organospecific carcinogenic effects, clearly dependent on chemical structure. The regular induction of cancer of the oesophagus, lungs, urinary bladder, or brain is described, providing reliable experimental models. [The SOI® indicates that this paper has been cited over 1,040 times since 1967.]

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April 6, 1981

"These systematic studies are based on earlier quantitative experiments with the liver-carcinogen 4-dimethylaminoazobenzene, known as 'butter yellow.' It was observed that at lower daily dosage the induction time increased up to the life span of rats The total dose required did not increase, but became significantly smaller.[1] This surprising result indicated that the primary effects of all individual doses are not only irreversible but also transmitted to daughter cells and, thereby, 'genotoxic '

"After the war, an otherwise precarious situation permitted a unique full-time cooperation with the electrophysicist K. Küpfmuller in elaborating the theoretical pharmacokinetic and ergokinetic bases for both the understanding of the former results and the systematic planning of new experiments. Their practical performance was then supported by the Deutsche Forschungsgemeinschaft.

"The great chance for comprehensive studies came in 1956, when the carcinogenicity of dimethylnitrosamine was discovered by P. N. Magee and J M. Barnes.[2] The simple molecule, ON-N $(CH_3)_2$, is enzymatically demethylated in the liver, yielding an alkylating intermediate, which explains the production of liver cancer However, preliminary experiments of D Schmahl and R Preussmann demonstrated that diethylnitrosamine has the same effect. This suggested that the first step in metabolic activation is probably an enzymic hydroxylation at one alpha C-atom, which then automatically leads to dealkylation. Accordingly, all the various dialkylnitrosamines, susceptible to alpha C-hydroxylation, should be carcinogenic. Furthermore, since some of the hydroxylases might be organo-or substrate-specific, specific effects could also be expected. The idea was extremely fascinating, first, because organosnecific effects, so fundamental in all pharmacology, are most easily recognizable in carcinogenesis and, second, because the group of N-nitroso-compounds is extraordinarily versatile, permitting an easy synthesis of innumerable derivatives and, thereby, systematic studies on relations between chemical structure and both efficacy and organospecificity. Expectations were surpassed by the experimental results. Surprisingly, striking organotropic effects were likewise observed with alkyl-acyl-nitrosamides, which don't need any enzymic activation to yield an alkylating intermediate. For example, with methylnitrosourea we succeeded for the first time in inducing cancer in the central organ, the brain, with an accuracy formerly considered unimaginable

"The results of quantitative studies on the relations between dose (d) and induction time (t), extensively performed with diethylnitrosamine, confirmed that carcinogenesis obeys so simple a formula as $d\ t^n = const$. This is indeed perplexing, but natural regularities are necessarily simple. Since the numeric value of n was always greater than two, it corresponds to an accelerated process. Accordingly, the induction of cancer by one single dose or 'impulse' was demonstrated on several examples and, most convincingly, in transplacental experiments with ethyl-nitrosourea, mainly performed by S Ivankovic. Although the dose was small and not toxic to the pregnant rat, practically all offspring later died with cancer of the brain and nervous system, which demonstrated the extreme vulnerability of the nervous organs during prenatal development.

"The worldwide interest the paper still enjoys is not surprising for four reasons: first, it provided reliable experimental models for almost all types of cancer; second, the biochemical mechanism of action is transparent; third, there are still numerous N-nitroso-compounds to be studied; and, last but not least, these carcinogens are easily formed by reaction of alkylamines or -amides with nitric acid, widely distributed in the human environment. It is hoped that the paper will contribute to the main goal: cancer prevention. More recent work is reported in 'Chemical carcinogenesis on N-nitroso derivatives.' "[3]

1. **Drackrey H & Küpfmüller K.** Quantitative Analyse der Krebsentstehung. Z. *Naturforsch.* **3**:254-66, 1948.
2. **Magee P N & Barnes J M.** The production of malignant primary hepatic tumours in. the rat by feeding dimethylnitrosamine. *Brit. J. Cancer* **10**:114-22, 1956.
3. **Druckrey H**. Chemical carcinogenes on N-nitroso derivatives. *GANN Monogr. Cancer Res.* **17**:107-32, 1975.