THE ROLE OF HYDROXAMIC ACID ESTERS FOR THE GENOTOXIC EFFECTS OF TRANS-4-ACETYLAMINO-STILBENE. E.Zielinski and H.-G.Neumann. Institute of Pharmacology and Toxicology, University of Würzburg, Versbacherstr. 9, 8700 Würzburg, F.R.G.

Metabolites of trans-4-acetylaminostilbene (trans-AAS) produce nucleic acid adducts in various rat tissues. We have now tentatively identified the major adduct from liver RNA. It is identical with an adduct formed from N-acetoxy-trans-AAS and guanosine in vitro. The acetamido-group is preserved and the stilbene moiety is attached to the base through the two carbons of the stilbene bridge, forming an imidazolidine ring. This adduct is stable and persistent in vivo, but decomposes upon hydrolysis of nucleic acids into several distinct products, which account for a number of adducts hitherto contained in nucleic acid hydrolysates. The results indicate that these adducts are major constituents of modified RNA and DNA in vivo. This would imply that esters of N-hydroxy-trans-AAS contribute to the genotoxic effects associated with tumour initiation.

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NATURAL CYTOTOXICITY IN VIVO CHARACTERIZED IN A NON-IMMUNOGENIC RAT TUMOUR.
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The actual anti-tumour activity of natural defense mechanisms in vivo (NK cells and Mø) precludes itself from ready analysis - especially in the rat - because of the lack of selective depletion regimes. This limitation was essentially overcome in the present system by 1) the use of non-immunogenic tumour lines with differential in vitro sensitivity towards natural cytotoxic effectors; 2) elimination of NK and Mø-functions by irradiation and silica treatment; 3) evaluation of tumour cell survival by short-term monitoring of ^{125}IUDR excretion.

It was observed that the fate of susceptible tumour cells was indeed determined by the activity level of natural cytotoxic cells in a dose dependent manner, provided that immediate contact of tumour and effector cells was achieved (i.e. in the peritoneal cavity). Tumour cells with low susceptibility in vitro were nevertheless eliminated in vivo. Cells injected into the bloood stream were quickly killed by a mechanism which was insensitive to irradiation and silica.

It is concluded that the local situation has a dominating influence on the actual efficiency of natural cytotoxicity. The fate of tumour cells in the blood depends on yet another principle of cell destruction.

ADAPTATION OF NON-IMMUNOGENIC TUMOURS TO NK CELLS
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The question whether adaptive loss of suceptibility to natural cytotoxicity occurs upon prolonged exposure of tumour cells to the respective effector cells was addressed in vivo and in vitro. In vitro treatment was without effect despite a regimen eliminating greater than 99.9% of susceptible target cells. Interaction in vivo (i.p.), however, led to an irreversible change in susceptibility which was conserved after retransplantation of ascitic cells to a subcutaneous site. Clonal analysis of tumour cells before and after "adaptation" to ascitic growth revealed homogeneity, thus arguing in favour of true adaptation as opposed to selection of pre-existing variants.

In one tumour line, transplantation of ascitic cells to a subcutaneous site gave rise to a locally growing susceptible and a metastasizing non-susceptible subline. This finding is interpreted as an exception because of further peculiarities with respect to general lysability by immune mechanisms, surface structures and karyotype.