Informal Discussion following the Paper by Pour *et al.*

Dr. Mohr: May I add some data using diisopropanolnitrosamine (DIPN) in the rat as a host species. As you know, the work on hamsters presented by Dr. Pour was performed at the University of Nebraska Medical Center. At the same time in Hannover, we have been doing parallel studies in rats. The compound was supplied by Dr. F. W. Krüger from the German Cancer Research Center in Heidelberg.

After determining the 50% lethal dose (LD_{50}) for DIPN in Sprague-Dawley rats (7125 mg/kg body weight for both sexes), 5 groups, each with 30 rats (15 males and 15 females), were treated s.c. according to the following scheme: $\frac{1}{5}$ LD_{50}, 1426 mg/kg body weight; $\frac{1}{10}$ LD_{50}, 713 mg/kg body weight; $\frac{1}{20}$ LD_{50}, 356 mg/kg body weight; $\frac{1}{40}$ LD_{50}, 128 mg/kg body weight; controls, olive oil vehicle.

All animals were treated once weekly for 20 weeks. The experiment is now in its 50th week after beginning treatment, and all animals in the groups treated with $\frac{1}{5}$, $\frac{1}{10}$, and $\frac{1}{20}$ of the LD_{50} have died. Most tumors in the highest dosage group were found in the liver (hepatocellular carcinoma and hemangioendothelioma), nasal cavities (squamous cell papilloma and adenocarcinoma), thyroid (adenoma and adenocarcinoma), esophagus, and lungs (adenoma, squamous cell carcinoma). Only 7% of the male rats developed pancreatic tumors. The lower the dose administered, the greater the incidence of nasal cavity tumors which infiltrated the brain. The number of tumors developing in the thyroid greatly increased in the last dosage group. Tumors of the renal pelvis (squamous cell carcinoma and papilloma) occurred in only the groups receiving either $\frac{1}{5}$ or $\frac{1}{10}$ of the LD_{50} (Figs. 1 to 4).

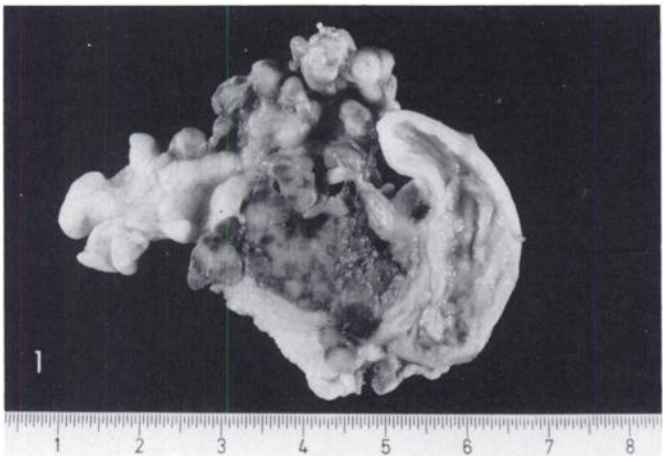

Fig. 1. Pancreas tumor of a male Sprague-Dawley rat, 30 weeks after beginning treatment with DIPN, 713 mg/kg body weight (1/10 the LD_{50}), s.c. once weekly for 20 weeks. The tumor mass infiltrated the pyloric part of the stomach. The neoplasm was more than 35 mm long and was histologically diagnosed as a poorly differentiated adenocarcinoma. Scale used in figure is in cm.

Dr. Weisburger: This is a perfect example of international collaboration; your group deserves our congratulations and gratitude. For the 1st time we have a good animal model for ductal pancreas cancer. As we develop data about usable dose levels, we may be able to induce this cancer in the pancreas in other species. We seem to be dealing with a multipotent carcinogen and a competitive situation as to which organ is affected first.

I have a short question for Dr. Pour. Did you find a relationship between dose of carcinogen and the specific area of the pancreas affected? I believe that you had shown a localization of the lesions by the area affected, but not in relation to dose. In other words, at the lower dosage, did you find a preferential localization in 1 area of the pancreas?

Dr. Pour: We did consider the possible relationship between dose level and anatomical location, size, and morphological patterns of the induced tumors. However, the reexamination of our material in this regard failed to show such a relationship.

Dr. Fitzgerald: I also would like to add my congratulations to this group because, speaking from a recent survey of the human material, this looks like the best model so far that has replicated pretty much of the common forms of tumors that one sees in the human material. A quick look at these slides shows about every pattern of duct adenocarcinoma that we have described in humans. Of course, in the animal,

Fig. 2. Thirty-eight weeks after beginning of s.c. treatment with DIPN, 713 mg/kg body weight (1/10 the LD_{50}), bilateral thyroid gland tumors were macroscopically found in a female Sprague-Dawley rat. Histologically, the tumor in the right gland was an adenocarcinoma infiltrating the muscles of the larynx, while on the left side the neoplasm was an adenoma.

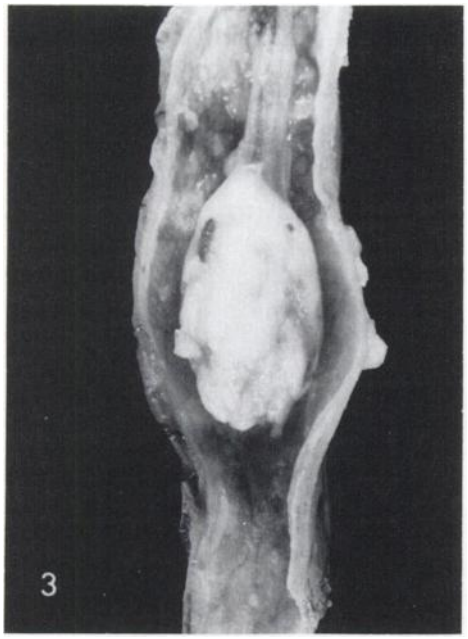

Fig. 3. Squamous cell papilloma obstructing the middle part of the esophageal lumen. The tumor was found in a male Sprague-Dawley rat 32 weeks after beginning of s.c. treatment with DIPN, 713 mg/kg body weight (1/10 the LD_{50}).

one may get all sorts of patterns and not necessarily the patterns that we see in the higher organisms. Since the model shows the features of the commonest forms I've seen in humans, I think this would be an excellent animal model to use.

Dr. Sporn: Dr. Pour, do you have any data at dose levels lower than 125 mg/kg twice a week? Do you have some selectivity for the pancreas as opposed to other sites at lower dose levels?

Dr. Pour: Not yet.

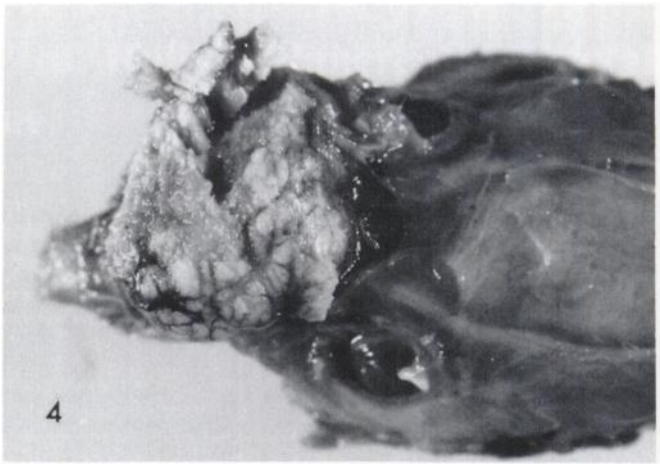

Fig. 4. Nasal cavity tumor destroying the nasal and frontal bone of a female Sprague-Dawley rat, 43 weeks after beginning treatment with DIPN, 356 mg/kg body weight (1/20 the LD_{50}). Histologically, the tumor was a poorly differentiated adenocarcinoma originating from the nasal cavity epithelium.

Dr. Saffiotti: A question to either Dr. Pour or Dr. Mohr. Dr. Mohr's laboratory developed in the last few years an experimental model, the large European hamster, which is a larger species than the Syrian hamster. I wonder if you have tried the DIPN on that species? If it worked, it would provide an anatomically larger species on which studies of localization and possibly studies of histogenesis might be easier.

Dr. Mohr: We are currently working on this. As you know, the European hamster is a hibernating species. We are interested not only in the differences between the 2 hamster species, but also in examining the influence of hibernation on cancer induction with these carcinogens. Metabolic processes during these different phases may have more than just a quantitative difference. I hope that at the end of this year I will be able to provide you with these results.