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General Discussion[1]

Dr. Weisburger: I think this is a good time to review this morning's session. Particularly, I make reference to Dr. Pour's comment in his important presentation, namely, that in light of his data he believes that isopropanolnitrosamine most likely reaches the pancreas via the blood directly.

This reminds us of a similar situation in colon carcinogenesis. In the past, some of us felt that a colon carcinogen reached the colon after absorption from the upper part of the gastrointestinal tract, metabolism in the liver, secretion of metabolites as conjugates in the bile, followed by liberation of active metabolites by bacterial enzymes. On the basis of the then existing data, it was felt that colon carcinogens affected the colon by such an indirect mechanism (Cancer, *28:* 60, 1971).

But, more recently, on the basis of what we have now learned with 1,2-dimethylhydrazine and azoxymethane, I think it is evident that the microbial flora plays a relatively minor role (Cancer Res., *35:* 287, 1975). It is very likely that this chemical does reach the colon via the blood, that it is activated by mammalian enzymes in the colon mucosa, and that cancer is the eventual result. On the other hand, we also know of other types of colon carcinogens, like 3-methyl-4-aminobiphenyl derivatives, which travel through the lumen and presumably are metabolized in the indirect mode discussed above (Diseases Colon Rectum, *16:* 431, 1973).

I would propose that, if 2 routes are possible in nature, both could be operative. With specific reference to the pancreas, is there or is there not some metabolite of specific carcinogens that gets into the pancreas by bile reflux? This is possible and requires experimental documentation.

I think we need to consider that it is possible or even probable that diisopropanolnitrosamine reaches the ductal cells from the blood. However, in the experiment of Dr. Reddy, I don't quite visualize blood as a carrier. Thus there may be several ways of transport for different carcinogens to the target. We have to be very open-minded and begin to collect data.

I would suggest to our clinical colleagues that in the next thousand autopsies they look for the possible connection between bile and pancreatic ducts. Dr. Fitzgerald mentioned he did not see any evidence for this in his material. In animal models, this does occur. Man is heterogeneous. In our presentations today, we have in fact noted a connection between the bile duct and the pancreatic duct in 6% of the cases. It could be that those are the individuals who have a higher risk of pancreatic cancer. I think it behooves us, in the future, to look at the human material and study our animal material and do careful autopsies. I venture to say that, in past work in liver carcinogenesis, we rarely looked at the pancreas if it "appeared normal" grossly. Nonetheless, with some chemicals, *e.g.*, aromatic amines, we might have seen early lesions in this organ. In view of the tremendous national interest in pancreatic carcinogenesis, we ought now to look at the pancreas much more carefully and to study these various modalities and mechanisms, so that in the next few years we can have answers to some of these questions.

Dr. Fitzgerald: Dr. Scarpelli, are you going to isolate and examine nuclear and plasma membranes for their alteration under the influence of this mitogen?

Dr. Scarpelli: Yes, since we now have tritiated methyl sterculate, we plan to study its incorporation into cell lipids, cell membranes including the plasma membrane, and nuclear membrane.

I would like to ask a question of anyone who can answer it. Has anyone studied the pancreas in terms of its capacity to metabolize chemical compounds? It is so well endowed with rough-surfaced endoplasmic reticulum that one never thinks of the smoothed-surfaced variety in pancreatic cells. Is it there, is it capable of being induced, and can it carry on any of the detoxification reactions that have been so well studied in liver?

Dr. Longnecker: I don't have the answer, but I can report a stab at it in relation to attempting to activate known liver carcinogens in relation to bacterial systems for demonstrating mutagenicity. We have compared microsomal fractions from pancreas and liver. The pancreas was negative in relation to acetylaminofluorene, and the liver was positive.

Dr. Scarpelli: Is this after having primed the animal with compound?

Dr. Longnecker: I don't recall that we did. We did prime with phenobarbital in some instances, but I don't know if we did in this case.

Dr. Farber: There is no *a priori* reason why the pancreas won't respond, since most tissues do.

Dr. Wynder: I mentioned this morning that, while taking the history, we should also get a minimum amount of metabolic data on each patient. I have noticed that in most hospitals throughout the country, including cancer hospitals, we do not take blood lipids. It seems to me with all the money we spend on working up patients, blood lipids should be obtained especially since they have been shown to relate to coronary disease.

I would like to make a plea to those who will have influence on cancer centers. In addition to getting a good history, we should also get a minimum amount of labora-

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tory data on all of our patients. Such information is really much cheaper and often more pertinent than the more complicated animal studies that we are doing.

Dr. Pledger: Dr. Wynder, when you say "metabolic data," do you refer primarily to lipid metabolic parameters?

Dr. Wynder: This is just one aspect; you can of course get more information. I emphasize blood lipids because they are simple to do.

Dr. Scarpelli: I agree wholeheartedly; we should strive for a better workup of the patients and also of patient material such as tissues and body fluids.

I would like to return to Dr. Sporn's earlier question about electron microscopy of pancreatic cancer. It is embarrassing that most surgical pathologists are so involved in rendering a diagnosis for the surgeon in order that he can institute the appropriate therapeutic modality that questions like the one Dr. Sporn has asked will never be answered unless they prepare appropriate material for ultrastructural study almost as a routine procedure.

It would be very important to study *in situ* lesions of pancreatic ductal and acinar tissues and to compare these with the more advanced lesions of pancreatic cancer. Such studies will ultimately establish the histogenesis of pancreatic cancer. I tend to agree with Dr. Farber that acinar tissue should not be dismissed as the tissue of origin for pancreatic cancer since acinar and ductal epithelium are closely related embryologically.