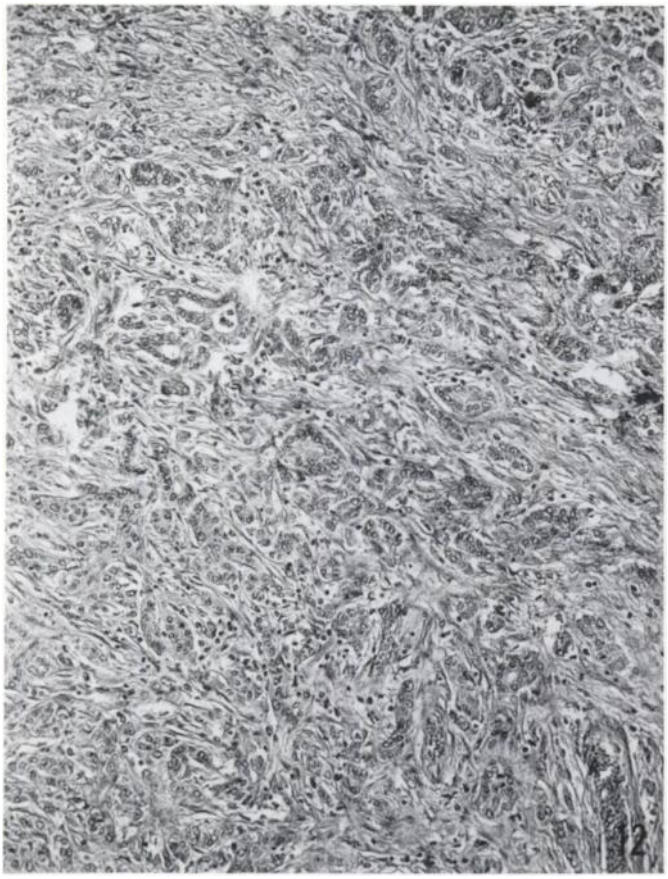

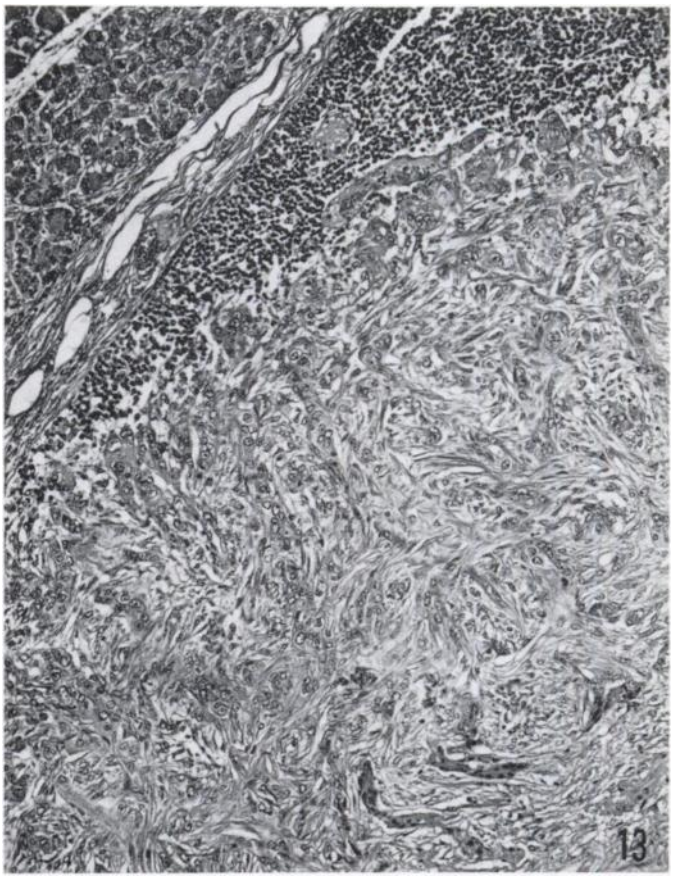

# Informal Discussion following the Paper by Reddy and Rao

**Dr. Fitzgerald:** I think we have 2 models now that simulate the pancreas cancers seen in the human. I would have a small caveat with Dr. Reddy because, where he shows acinar cells in the dilated ductule areas, he implies that duct cells arise from acinar cells. I don't believe this, because the identical picture is seen if you tied off splenic pancreas segment duct as we did some years before. Did you do electron microscopy in these suspected areas?

**Dr. Reddy:** No, we have not done ultrastructural studies of these areas.

**Dr. Fitzgerald:** I think one of the big problems in pathology arises when you begin to "see" transition cell types. Propinquity is unreliable in this area. Admittedly, it would be scientific cuckoldry to ignore the juxtaposition of cell types, but it is extremely difficult to interpret these anatomical relationships in precursor or transitional terms. I doubt that acinar cells transform into duct cells. I believe that acinar and islet cells are pretty much the end of the trail in terms of differentiation. So far, "dedifferentiation," if it exists, is a rare event in animals (if dedifferentiation means that the cells are starting out at the end of differentiation and going back to the primitive cell of origin). I would suspect that the duct cells might be able to differentiate into islet and acinar cells but the reverse, acinar cells to duct cells, I rather doubt. I've never seen an example of it in experimental pancreas studies. Otherwise, I think this a very fine model and one which will have considerable value.

**Dr. Reddy:** Thank you for your comments. I do realize that the question of dedifferentiation, particularly in pancreas, is a very difficult problem to prove. However, the illustrations shown here (see Figs. 5 to 7 of the preceding paper) strongly suggest that acini are capable of transforming into, at least, pseudoductules.

**Dr. Preussmann:** I would like to comment on the high mortality in your experiments. You also indicated that a possible explanation for low tumor incidence in our experiments in Germany was that the compound was administered in the drinking water and that decomposition of the carcinogen could have occurred. I think that this is not true. Our animals were housed overnight without water, and the

1st thing in the morning they were given a freshly prepared solution of the compound. This they usually drank within 2 hr. Within those 2 hr, it was shown that there was decomposition of less than 10%.

I think the reason for your high mortality is that your dosage is too high. You are giving the total dose in a single application, and perhaps you might avoid such a death rate by reducing such a dosage.

**Dr. Reddy:** That's a possibility. We were thinking about that. We may have better luck if we reduce the MNU dose to 5 mg/kg body weight, instead of the 10 mg as in the present study. Experiments with 5 mg/kg body weight are in progress.

**Dr. Farber:** Dr. Fitzgerald's comments have stimulated me and I feel compelled to reply. I think one has to think much more flexibly now than previously. You can't think in terms of here is a duct, and there is an acinus, and that's it. The 2 are entirely separate in all respects.

As is well known, during pancreatic regeneration one sees tiny duct-like structures, not acini. You don't see many acini with zymogen granules. There are duct-like areas, and from them develop the mature acini. So, I don't think one can really take the static, classical position of a morphologist.

**Dr. Fitzgerald:** Yes, one should be flexible, but he shouldn't ignore realities. We showed in regeneration of the pancreas after ethionine that regeneration of acinar cells comes only from the reversibly damaged acinar cells. Regenerating cells had a marker, an ethionine-produced ergastoplasmic lesion, whereby one could identify the regenerating cells as acinar cells. Duct cells only rarely had this marker. We measured the amount of regeneration of the duct cells by autoradiography and [$^3$H]thymidine, and that only went up by a factor of 3 to 4 and remained elevated for only a few days. The acinar cell labeling went up 20 times the control and remained elevated for at least 2 weeks. Only such an increase of DNA synthesis could account for the remarkable degree of pancreas regeneration. So I would suggest, on the basis of these studies, that regeneration of the acinar cell, and not the regeneration of the duct cell, is the basis for the pancreas regeneration after ethionine (Am. J. Pathol., *53:* 983–1065, 1968).