Informal Discussion following the Paper by Cubilla and Fitzgerald

Dr. Wynder: In your abstract, you mention differences in distribution of adenocarcinoma of the pancreas between head, body, and tail. My question is, does this give you a clue in terms of etiology, particularly because, as you know, in islet-cell cancer the distribution is 1:1:1?

The 2nd point is that we are obviously aware that the diagram shown is not the common anatomical relationship, but in the literature a common duct is described to occur with various frequencies.

But, even if it happens only in 6% of the cases, are these the cases that prevail in pancreas cancer, or is it impossible for us to make that statement because in most cases the ductal system is destroyed by the time the patient comes to the pathologist?

Dr. Fitzgerald: Let me take your last point. I think what you say is true; by the time one has a pancreas cancer surgical specimen, obviously, sometimes it's quite difficult. So, we went into this very carefully. In practically all of our cases, there was no common channel of the pancreas duct entering the common bile duct.

The range of cases in which the pancreas duct enters the common duct varies from 0 to 60 to 80% or higher in some studies. The average is 6% in the most detailed definitive studies, as Berman has shown with vinyl casts of the duct system, a true common channel exists in only 6% of cases (Berman *et al.*, Surg, Gynecol. Obstet., *110:* 391, 1960). Yes, our ratio is about 2:1, about twice as many cases in the head as in the body and tail.

I would like to think as Dr. Wynder does that reflux of bile causes cancer of the head of the pancreas. But I believe that is a little too simplistic, and I would prefer to think that the localization in the head merely indicates concentration of some carcinogen going down the pancreas duct, but that may be naive too.

Dr. Wynder: The 3rd question, related to the distribution of pancreatic cancer, is the areas of the head, body, and tail which are different somewhat from what you find for islet-cell cancer. Does this distribution give us a clue in terms of etiology? Also, I am not particularly sold on the bile reflux theory. I am just suggesting it as one of the possibilities that need to be considered.

Dr. Fitzgerald: There is 1 feature that I didn't emphasize which I probably ought to emphasize. I didn't realize there was this much *in situ* carcinoma (in about 20% of cases), although there is *in situ* carcinoma in every type of cancer, practically, of which we know. There might be an interlude of many years between the appearance of *in situ* cancer and the appearance of the gross tumors, somewhat analogous, say, to carcinoma of the uterine cervix, where you know the peak incidence of *in situ* cancer occurs years before the peak of invasive carcinoma.

This is probably something worthwhile focusing on; maybe 1 type of profitable study, a very tedious one, would be to get groups at high risk, focus on them, and try to find carcinoma *in situ* of the pancreas at autopsy. Dr. Wynder suggested this, and I think it would be worthwhile if the epidemiologist would spot groups at high risk.

Dr. Sporn: Dr. Fitzgerald, have you done any electron microscopy on these very interesting precursor lesions that you have talked about? Do you have any type of marker that might be useful in identifying these *in situ* or hyperplastic lesions?

Dr. Fitzgerald: Unfortunately, no. We are just beginning an electron microscopy study. We've looked at cases to decide whether most of the lesions are acinar or duct cell in origin. One of the problems is that to spot these *in situ* areas grossly is very difficult; you make take hundreds of sections to get a couple of little foci. But I think that this should be done.

Dr. Saffiotti: I would like to ask you to discuss the morphological distribution of these lesions within the pancreas tissue. What is the size of the carcinomas? I suppose that some of them are already large and invasive, but how many do you have that are relatively small so that you can localize their site of origin; and particularly, how far do you see the *in situ* lesions around the tumor? Is it a matter of a few mm or cm around the tumors, or do you have, for example, a large nodule in the head and then some precursor lesions also spreading in part of the tail? What are your feelings on the topographical correlations of these lesions in terms of multiple origins?

Dr. Fitzgerald: Well, unfortunately, our tumors are large and this is not as good a model as the experimental animal where you can select multiple areas. Sometimes we are confined to merely a section of the pancreas. But in those where we have the total pancreas, or a subtotal resection, a Whipple type of operation, we have looked at many blocks and sections, but in practically all of our cases the *in situ* lesions that we have seen to date have been within a couple of cm of the primary lesion. In the 2 exceptions, cases of the carcinoma arising in the head of the pancreas, there were obvious foci of carcinoma *in situ* out in the body and tail. This is a small percentage. Why we don't see more may be a matter of sampling.

In most of our cases, the resident would take only a few sections, although all our fellows are board-qualified pathologists when they come with us, and some have quite a bit of training. Still most are not and have not been too interested in the pancreas. One will get 4 or 5 slices of the primary tumor, 1 through the tail and 1 through the body. So our material has been limited.

Now, we are doing rather careful studies where we take

50 or 60 sections of a whole pancreas, but even that is selective and the pancreas is a large organ.

I think you remember some work that Drs. Foote and Stewart (Cancer, *1:* 431–440, 1948) at Memorial did: that if you took 4 sample quadrant biopsies of the cervix, you would pick up over 90% of the *in situ* lesions but if you took only 1 then you only picked up 48% of these lesions. The cervix is relatively small compared to the pancreas. So, I don't know whether this lack of finding more *in situ* pancreas lesions is merely a matter of poor sampling, or whether the lesion is not there. It is an extremely important question.

Dr. Reddy: Since there appears to be a close association between smoking and pancreatic cancer, it may be advisable to examine the pancreas of individuals dying of lung cancer. Have you looked at the pancreas of individuals with lung cancer? Did you see any *in situ* lesions?

Dr. Fitzgerald: Possibly Dr. Cubilla could answer. In the hundred control autopsies of patients with non-pancreas cancer that you looked for pancreas carcinoma *in situ*, were there any carcinomas of lung associated with heavy smoking?

Dr. Cubilla: Just 1. And in that case the pancreas was negative.

Dr. Fitzgerald: I don't know in that case if that was 1 section or more of the pancreas, more likely the former. We need more thorough examination of the whole organ in both surgical and autopsy specimens.