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Diabetologia

Letters to the Editor

The Pancreatic Polypeptide-Rich Lobe of the Human Pancreas: Definitive Identification of its Derivation from the Ventral Pancreatic Primordium

Sir,

The human pancreas, in common with that of most mammals studied so far, shows a very uneven distribution of two of the endocrine cell types, the glucagon- and the pancreatic polypeptide containing cells. Pancreatic polypeptide containing cells are concentrated in a posterior region of the pancreatic head which is extremely poor in glucagon cells [1]. This pancreatic polypeptide rich region often constitutes an individual lobe at the posterior and inferior pole of the head which can be cleaved along a connective-vascular plane from the remainder of the pancreas [2]. The embryological development of the pancreas, during which two distinct primordia merge to yield the definitive organ [3], suggested that the pancreatic polypeptide rich region has its origin in the ventral primordium [4]. Although this hypothesis was supported by studies of fetal and neonatal pancreas [5], direct proof has remained elusive. This is because pancreatic polypeptide containing cells are undetectable by immunocytochemical methods in the very early stages of development when the ventral and dorsal primordia are unfused. Pancreatic polypeptide containing cells become evident from week 10 of gestation onwards [6], at a stage when all trace of fusion has disappeared. By the systematic examination of the pancreas at autopsy from fetuses of various ages, we have discovered an annular pancreas which provides what we believe to be proof that the pancreatic polypeptide rich region has its origin in the ventral primordium.

Pancreases from legally aborted fetuses were fixed in toto in Bouin solution for 24 h, cut in three parts (head, body and tail) and separately dehydrated and embedded in paraffin. An annular pancreas was found in an 11-cm fetus, aborted during total hysterectomy for uterine leiomyoma. Horizontal paraffin sections of the head stained with hemalum-eosin confirmed that the duodenum was entirely surrounded by pancreatic tissue (Fig. 1A). Unstained sections (5 μm thick) were incubated with anti-bovine pancreatic polypeptide antiserum (dilution 1/200, a gift from Dr. R. Chance, Indianapolis). By using the indirect immunofluorescence method [7] to reveal the binding sites of the antiserum, it was possible to show immunofluorescent cells (Fig. 1B) in four-fifths of the circumference of the annular pancreatic tissue, but in none of the remaining one-fifth. In contrast, sections of the latter part showed numerous immunofluorescent cells (Fig. 1C) following incubation with an anti-glucagon antiserum (dilution 1/200, a gift from Dr. R. H. Unger, Dallas). On at least one side of the annular pancreas, the zone of transition between pancreatic polypeptide rich and poor regions was marked by an uninterrupted plane

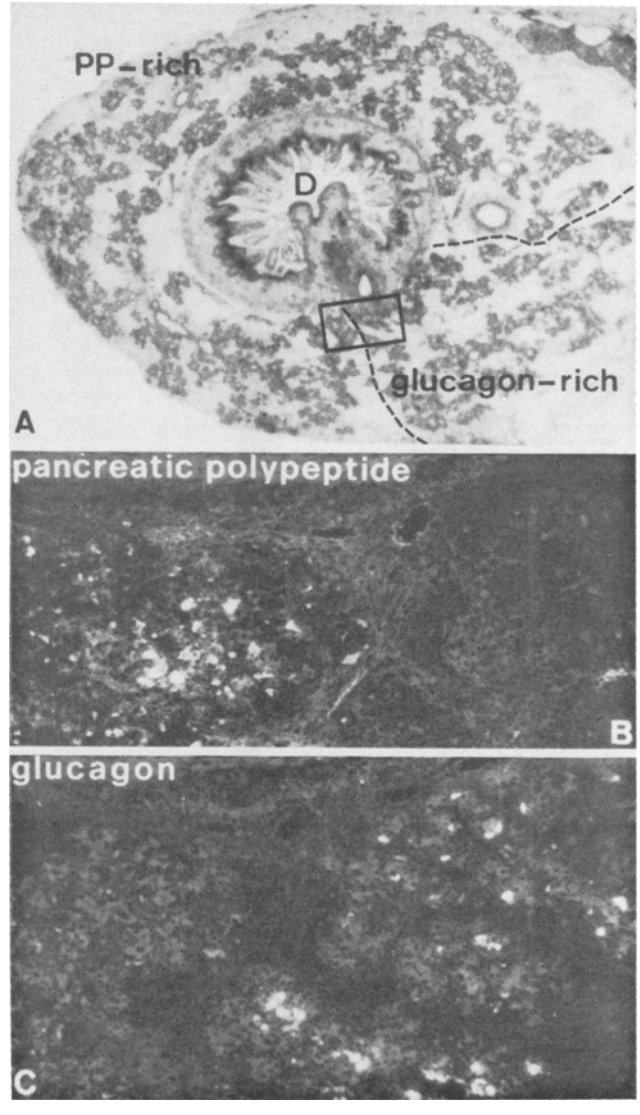

Fig. 1. Conventional and immunofluorescent staining of the annular pancreas. **A** Low power magnification (x 20) showing a transverse section of the duodenum *(D)* entirely surrounded by pancreatic tissue. The pancreatic tissue situated to the left of the two dotted lines contains numerous pancreatic polypeptide *(PP)* cells, while the tissue situated to the right of these lines shows numerous glucagon containing cells. The area comprised in the black rectangle is illustrated following immunofluorescent staining in **B** and **C**. The dotted lines represent the limits between the pancreatic polypeptide rich, ventrally derived, and the glucagon-rich, dorsally derived, regions of the annular pancreas (hemalum-eosin stain). **B** Higher magnification (x 100) of the region delimited by the rectangle in Part A in a section immunostained with anti-pancreatic polypeptide antiserum. Pancreatic polypeptide containing immunofluorescent cells are restricted to the left part of the field. **C** Higher magnification (x 100) of the region delimited by the rectangle in Part A in a section immunostained with anti-glucagon antiserum. The glucagon containing immunofluorescent cells are restricted to the right part of the field

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of connective tissue (dotted line Fig. 1A). An annular pancreas results from a defect in rotation of the ventral primordium towards the dorsal pancreatic bud [3]. The fact that all the abnormally-developed tissue showed a distinct pancreatic polypeptide immunofluorescence proves the hypothesis that the ventral primordium is the origin of the pancreatic tissue rich in pancreatic polypeptide. However, the reason for the differing pancreatic polypeptide and glucagon contents of the two primordia remains to be established.

Yours sincerely,

Y. Stefan, S. Grasso, A. Perrelet and L. Orci

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Exercise-Induced Proteinuria in Diabetic Children

Dear Sir,

The November 1981 issue of Diabetologia contained an article on exercise-induced proteinuria in children with Type 1 (insulin-dependent) diabetes [1]. In view of the results of studies on exercise proteinuria obtained in our laboratory, it would seem likely that the use of a radioimmunoassay as a means of estimating glomerular permeability in early diabetes may be providing correct, but less than optimal, information.

Polyacrylamide gel electrophoresis studies on the nature of the urinary proteins excreted after light exercise have shown that adolescent girls with normal renal function may excrete proteins of molecular weight as large as 170,000–215,000 daltons [2]. We have found similar size proteins in the pre-exercise urines of gymnasts, physical education students and rugby football players (unpublished observations). These findings have led us to conclude that, during everyday activities, large plasma proteins may pass through the glomerular filter. Such temporary increases in glomerular permeability are enhanced during exercise and the high molecular weight proteinuria will be associated with increased urinary protein concentration.

We have found that the urinary protein profiles of patients with the nephrotic syndrome are not very different from the post-exercise urinary protein profiles of healthy young athletes. Urine from diabetic patients, studied by the same technique, showed similar protein profiles to some post-exercise samples, but in those cases where the ESR was raised the urine contained larger plasma proteins. From this point of view, the difference between exercise proteinuria and pathological proteinuria appears to be the persistence and chronicity of the latter.

Recently I have proposed that increased blood viscosity is an important factor in the mechanism of proteinuria and capillary leakage [3]. As it has been well demonstrated that diabetic patients with poor metabolic control have increased blood viscosity, it is probable that, in circumstances where blood viscosity was even slightly increased, the intra-renal vascular changes associated with exercise would result in proteinuria. However if the excretion of albumin alone was being monitored then the significance of the proteinuria might be missed. It seems likely that those diabetic patients with raised basal urinary albumin levels who showed marked increase in albuminuria after exercise [4] also had raised blood viscosities. As normalisation of blood viscosity occurs when good metabolic control is restored in diabetes, the removal of the cause of chronic proteinuria will not prevent temporary high molecular weight proteinuria occurring after athletic activity.

In order to utilise recently published information in the fields of exercise proteinuria and haemorheology, I would suggest that, where possible, studies of 'diabetic' proteinuria should include investigations into low shear rate blood viscosity.

Yours sincerely

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