results — we took it early when the patient came to haemodialysis and when the patient was stable on haemodialysis. Can you confirm his results in these terms?

GRIMMEL No, I have no experimental studies as such. I have looked for the enzyme in acute uraemia and I have seen nothing — but this was total nephrectomy.

CHAIRMAN If there are no more questions we will hear the paper by Dr Wizemann. He will speak about the functions of exocrine pancreas in renal failure.

EXOCRINE PANCREATIC FUNCTION IN CHRONIC RENAL FAILURE

V Wizemann
Zentrum für Innere Medizin, Giessen, GFR

Because the metabolic activity of the exocrine pancreas is high — an acinar cell for example daily synthesises its own weight of protein — the gland is secondarily involved in many diseases. As shown by Baggenstoss (1948) chronic renal failure causes severe morphologic alterations of the pancreas, which are different from chronic pancreatitis. Conflicting clinical results have been published by Bartos et al (1970) and by Schmidt et al (1969) concerning pancreatic fluid secretion and enzyme output in the uraemic state. Recently Otte et al (1975) showed, by the aid of computer analyses, that pancreatic secretion might be specifically changed in patients suffering from chronic renal failure. These patients could be differentiated by their secretion pattern from normal controls, and patients with chronic pancreatitis, pancreatic carcinoma, acute and chronic duodenal ulcer.

The trigger for the research on uraemic pancreatopathy is the elevated serum lipase activity often found in patients with chronic renal failure (Figure 14), indicating possible damage to the pancreatic cells (Otte et al, 1975; Wittich et al, 1968). Heidbreder et al (1976) found a close correlation between the degree of renal insufficiency and serum lipase activity. A statistical comparison of laboratory data with the serum lipase data revealed that anaemia and acidosis correlate with hyperlipasaemia. Other clinical findings such as an elevated faecal fat excretion and decreased chymotrypsin content of the stool (Figure 15) additionally indicate pancreatic alterations in the uraemic state.

In order to study the phases of pancreatopathy during the development of uraemia, animal experiments have been performed with chronically uraemic rats (Heidbreder et al, 1974; Wizemann et al, 1974a). Compared with a control group, exocrine pancreatic secretion increases gradually with elevated serum urea concentrations (Figure 16).
Figure 14. Serum lipase activity in renal failure

Figure 15. Daily stool fat excretion and chymotrypsin content of the stool in chronic renal failure
At urea levels of about 170 mg/100 ml pancreatic fluid secretion, as well as enzyme output, are nearly twice as high as the control values. Referred to the wet weight of the gland, the secretion data are in the same range, indicating hypertrophy of the pancreas in this phase (Wizemann et al, 1974b). Histochemical studies (Gladisch & Krempien, 1976) confirm an initial increase of metabolism in the uraemic acinar cell. To elucidate the pathogenetic mechanism of pancreatic hypersecretion in the first phases of chronic renal insufficiency, the "stimulus – secretion" system of pancreatic fluid secretion was tested. As demonstrated by Case (1973), pancreatic fluid secretion is controlled by the cyclic AMP system. It could be shown that in the first phases of uraemia, basic, as well as secretin or fluoride stimulated adenylate-cyclase activity, is about five times higher than in normal controls (Wizemann & Glossmann, 1976). Decreased secretin inactivation by the failing kidneys, as proposed by Lehnert et al (1975) could be ruled out for the rat (Wizemann et al, 1974b).

In the end stage of renal failure, pancreatic secretion volume as well as lipase and amylase secretion is reduced (Figure 16). To study the role of "toxins" accumulated in severe uraemia, perfusion experiments have been performed with an isolated pancreas according to the method of Case et al (1968). Methylguanidine in a concentration of $10^{-5}$ M/l inhibits pancreatic secretion reversibly (Figure 17) and the same holds for 2-hydroxyphenylacetic acid. Middle molecular substances failed to influence the secretion rate. Since the exocrine pancreatic cells are well equipped with ATPase systems (Wizemann et al, 1974c), which
Figure 17. Effect of methylguanidine $10^{-5}$M/l (white bars) on the isolated perfused pancreas
could be involved in the active electrolyte transport of the gland, small molecular uraemic ‘toxins’ have been tested on ATPase activity.

Na\(^+\)-K\(^+\) ATPase, bicarbonate-stimulated ATPase (Simon et al, 1972) and Ca\(^++\)-stimulated ATPase are inhibited by the different ‘toxins’ (Table IV). In addition

**TABLE IV. Effect of Small Molecular Uraemic ‘Toxins’ on Pancreatic ATPase Determined in a Membrane Fraction of Cat Pancreas**

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Conc. (M/l)</th>
<th>Inhibition m (%)</th>
<th>SE (%)</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+)-K(^+)-ATPase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>methylguanidine</td>
<td>(10^{-4})</td>
<td>14.00</td>
<td>5.91</td>
<td>5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>4-aminobenzoic acid</td>
<td>(10^{-5})</td>
<td>23.50</td>
<td>13.24</td>
<td>6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>2-hydroxyphenyllic acid</td>
<td>(10^{-5})</td>
<td>31.00</td>
<td>9.50</td>
<td>5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

| Mg\(^{++}\)-ATPase          |             |                  |        |    |       |
| methylguanidine              | \(10^{-4}\) | 1.04             | 0.57   | 5  | >0.05 |
| 4-aminobenzoic acid         | \(10^{-5}\) | 0.46             | 0.33   | 5  | >0.05 |
| 2-hydroxyphenyllic acid      | \(10^{-5}\) | 0.88             | 0.98   | 5  | >0.05 |

| HCO\(^{-3}\)-ATPase         |             |                  |        |    |       |
| methylguanidine              | \(10^{-4}\) | 24.20            | 3.32   | 5  | <0.01 |
| 4-aminobenzoic acid         | \(10^{-5}\) | 21.10            | 3.19   | 9  | <0.01 |
| 2-hydroxyphenyllic acid      | \(10^{-5}\) | 2.10             | 1.93   | 9  | >0.05 |

| Ca\(^{++}\)-ATPase          |             |                  |        |    |       |
| methylguanidine              | \(10^{-5}\) | 19.23            | 4.44   | 11 | <0.01 |
| \(10^{-4}\)                |             | 21.31            | 5.63   | 11 | <0.01 |
| 4-aminobenzoic acid         | \(10^{-5}\) | 27.58            | 8.13   | 11 | <0.01 |
| 2-hydroxyphenyllic acid      | \(10^{-5}\) | 23.35            | 3.96   | 11 | <0.01 |

to the effect of the ‘toxins’, pancreatic hyposcretion in the final phase of uraemia can be due to many factors which influence the secretion rate: reduced oxygen supply (Wizemann & Schulz, 1973), calcium ion concentration (Argent et al, 1973), acidosis (Case et al, 1968) hyperparathyroidism (Cope et al, 1957).

There is still one remaining question: is the elevated serum lipase activity in the uraemic state an indicator of an acute or chronic pancreatitis? The high serum amylase activity described by Levitt et al (1969) can be attributed to diminished renal clearance in uraemia. As shown in Figure 18, serum amylase activity is elevated after ligation of the renal vessels for one hour. The same holds after the ligation period, while pancreatic fluid secretion and the amylase and lipase content in the juice were unchanged. Since lipase activity cannot be measured in the urine, it can be assumed that the kidneys, which have many

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aminopeptidase activities (Mattenheimer et al, 1964), are able to inactivate the lipase enzyme. In renal failure this function may be impaired too, and failure of inactivation of serum lipase may lead to a harmless hyperlipasaemia.

References

Case, RM (1973) Acta hepato-gastroenterologica, 20, 435
Open Discussion

CHAIRMAN This paper is now open for discussion. Are there any questions for Dr Wizemann?

HABERAL (Ankara) I do not know how many patients get acute pancreatitis on chronic haemodialysis, but I think quite a few patients after transplantation develop acute pancreatitis. I would like to ask one question: what is the uraemic toxin?

WIZEMANN I am cautious; I have said the so-called 'uraemic toxins', and we have tested phenols, methyl guanidine and 4-amino benzoic acid. We have also tested the effect of middle molecules on pancreatic secretion in our perfusion experiments and we did not see any effect of the middle molecules on pancreatic secretion.

KASPER Dr Wizemann, we looked for lipase activity in totally nephrectomised patients and did not find any elevation of the lipase activity. Did you look at such patients?

WIZEMANN No, we are just about to investigate whether lipase is inactivated in the kidneys in man, by determining activity in the renal artery blood and in the renal venous blood.

KASPER But it should be elevated if you have a totally nephrectomised patient.

WIZEMANN Yes, it should be elevated, that is right. It may be that the lipase is inactivated by the many amino-peptidases which are located in the kidney, and it may be that it goes through the glomerular membrane and is inactivated along the tubule; the amino peptidases have been shown to be located in the luminal side of the kidney cells.
KASPER You did not nephrectomise rats and look?

WIZEMANN No, we ligated the artery and the renal vein.

LÖHRS To Dr Haberal from Turkey, I think we should keep in mind that pancreatitis is not so very common in renal failure or in transplantation. It is a change which is not pathognomonic, but we may say characteristic, with acinar dilatation and interstitial fibrosis with only scanty inflammation and that might be one of the reasons in late renal insufficiency that there might be a pancreatic insufficiency too. One remark to Dr Wizemann: in the complex regulation system of stomach, pancreas and duodenum, I think the findings of the Munich group are very interesting. They found that the gastrin level is elevated and gastrin, as we know stimulates gastric acid and then secretin release is induced, so there might be an elevation of —

WIZEMANN You’re wrong, you’re wrong.

LÖHRS I am wrong?

WIZEMANN Dr Hesch may agree too, gastrin only stimulates the enzyme secretion of the pancreas.

LÖHRS Yes, but it stimulates gastric acid output and then by making the reaction acid in the duodenum, maybe secretin.

WIZEMANN Maybe, yes.

LÖHRS It is difficult to show this experimentally.

WIZEMANN Yes.

LÖHRS We were astonished to see this hyperactivity of adenylate cyclase, and we looked to see if this is the same in other organs, for instance in the heart, which is much more interesting, but we did not find it. Adenylate cyclase activity was the same as in the controls compared with uraemia, concerning the heart.

LORNOY (Aalst) From a clinical point of view it may be very difficult to make a diagnosis of acute pancreatitis in chronic renal failure. How can you help us to make a possible diagnosis?

WIZEMANN I have no idea, the only thing I can say is hyperlipasaemia is not a valid diagnostic criteria of the development of pancreatitis during uraemia. You have to look for clinical signs but all uraemic patients have pain in the stomach and in the abdomen, and it is very difficult.

HABELAL I cannot remember exactly the number, but probably about 10% of transplant patients develop pancreatitis. Nobody knows really why these patients get acute pancreatitis. Is it related to prednisone dosage or calcium or something else?

KASPER I think the most important aspect is the therapy with immunosuppres-
sive agents and corticosteroids — they could induce acute pancreatitis in these patients.

DRUEKE I want to put one small question. Dr Wizemann, why do you think that there are normal lipase levels in anephric patients whereas you find high lipase levels in, let us say, anephric rats? When you ligate renal vessels these rats can be considered anephric. When you want to know whether it is the anephric state, that is the non-excretory function, or the non-parenchymal function, you have two experimental models. You have to compare bilateral nephrectomy with ureterocaval animals. How do you explain the difference between humans and the rats?

WIZEMANN Yes, there is also a difference between dogs and rats concerning secretin inactivation. Some groups say the hypersecretion of the pancreas is due to the inability of the kidneys to inactivate the hormone secretin, that is true for the dog but not true for the rat. Maybe there are differences between man and rats, but the only thing I can say is that somehow in the kidneys lipase may be inactivated, somewhere between the renal artery and the renal vein.

DRUEKE In the rat?

WIZEMANN In the rat.

KASPER I have one question to Dr Wizemann: you found steatorrhoea in your patients with renal insufficiency. How much fat was in the diet?

WIZEMANN 100 grams per day.

KASPER 100 grams?

WIZEMANN The same experimental conditions as yours.

KASPER Did you try substitution with pancreatic enzymes and see if it is possible to treat the steatorrhoea?

WIZEMANN It is only a slight steatorrhoea, with the mean between 10 and 16 grams of fat per day and one should try this.

KASPER Another short question. We looked for lipase activity in chronic renal disease, and we found that there was a difference in the elevation of lipase activity between diseases; cystic renal disease had relatively low levels of lipase, but glomerulonephritis had relatively high levels at the same degree of insufficiency. Did you find these differences too?

WIZEMANN No we did not find it. You know that in cystic disease of the kidney, there are some functions which are still good, for instance erythropoeitin secretion, and it may be the kidneys are only partially non-functioning.

CHAIRMAN If there are no more questions I thank you very much, and we close the session.