PATHOLOGICAL CHANGES IN PANCREAS AND INTESTINE IN RENAL INSUFFICIENCY

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Gastroenterological disturbances, such as nausea, vomiting and bleeding are characteristic of the uraemic syndrome. The pathomorphological changes seen in many organs, are not pathognomonic per se. Only by synopsis of all the changes recognised in the individual case, and by considering the clinical findings, may they be attributed to uraemia. Using the word uraemia in conjunction with morphological changes in pancreas and intestine, I am aware of the fact that there need not always be a fully developed uraemic syndrome to produce them.

Pathological changes in the pancreas and in the gastrointestinal tract can be severe complications in patients with renal insufficiency, in dialysis or in connection with kidney transplantation. The relations between histomorphology and the physiology of pancreatic secretions are schematically outlined in Figure 1.

![Figure 1. Simplified model of pancreatic secretion and its regulation](image-url)
For a simplified description it is sufficient to group the numerous pancreatic enzymes or enzyme-groups as proteochylus (Becker, 1973). The secretion of the proteochylus by the acinar cells is stimulated by pancreozymin/cholecystokinin (CCK), produced mainly in the lower duodenum and upper jejunum. Release of pancreozymin is induced by cholinergic effects and mainly by the ingesta (Becker, 1973; Demling, 1974). The second main component of pancreatic juice is the hydrochylus, consisting of water, electrolytes and particularly of bicarbonate. It is produced in the isthmic duct cells, which are rich in carbonic anhydrase. The acinar and isthmic cells are wrapped in a dense network of capillaries, an essential factor for their secretory capacity. The hydrochylus-secretion is stimulated by secretin, which is liberated chiefly in the upper, post-pyloric duodenum when the luminal pH is below a threshold of 4.5 (Demling, 1974). The extent of the intact small intestinal surface in contact with the stimulating factors correlates with the amount of secretin and pancreozymin liberated.

![Figure 2. Left: normal exocrine pancreatic parenchyma with acini and initial, isthmic, parts of ducts (arrow). Right: Acinar ectasia in azotaemia with interstitial fibrosis (arrow). (Original magnification circa x 300 — reduced for publication)](image)

What kind of relation is there between the physiology of the pancreatic secretion and the morphological changes recognised in azotaemia? Except for occasional cases of acute pancreatitis in uraemia (Geertruyden & Touissant, 1967) and after renal transplantation (Starzl et al, 1964; Tilney et al, 1966) the most significant pathological change in the pancreas is acinar dilatation (Figure 2, right). The ectatic acini are filled with an inspissated, eosinophilic and PAS-positive material, i.e. an inspissated proteochylus, rich in protein. Comparison with the normal pancreas clearly demonstrates the flattening and the atrophy of the cylindrical acinar cells, the apical parts of which are normally filled up with secre-
tory granules (Figure 2, left). In acinar ectasia, the acinous epithelia become partly necrobiotic. Probably as a consequence of the epithelial defects, interstitial oedema may develop, inducing a focal or diffuse interstitial fibrosis with usually only a scanty chronic inflammatory cellular reaction. These changes have sometimes been regarded as the cause of subclinical pancreatic insufficiency in patients with chronic or relapsing azotaemia (Stein & Powers, 1956).

In an extensive investigation of the pancreatic changes in renal insufficiency, Baggenstoss (1948) found acinous ectasia in 45% of 270 autopsies of patients with uraemia from various causes, whereas in the controls there was an incidence of 20%. This did not depend on the age of the patients nor the degree of azotaemia. As demonstrated by the relatively high incidence of acinar dilatation in the controls, the pancreatic changes are not pathognomonic for renal insufficiency. They seem to be the morphological manifestation of a non-specific metabolic disturbance. In several other investigations, incidences of 19% (Ball et al, 1950), 21% (Stein & Powers, 1956) and 41% (Warren & Sommers, 1949) of unselected autopsies, as well as 14% in children (Menten & Kinsey, 1949) have been found. Apart from azotaemia, pancreatic acinar ectasia can mainly be demonstrated in cirrhosis of the liver, cachexia and inflammatory intestinal diseases, particularly in ulcerative colitis, in which acinar dilatation has been found in 53–75% (Warren & Sommers, 1949; Ball et al, 1950). Generally, dehydration, electrolyte disturbances, protein deficit and irritation of the neural and hormonal stimulation of pancreatic secretion are considered as causative factors.

The pathophysiological factors in uraemic pancreopathy are summarised in Figure 3 (Baggenstoss, 1948; Stein & Powers, 1956; Bartoš et al, 1970; Becker, 1973; Fleischer & Kasper, 1974; Heidbreder et al, 1974; Otte et al, 1975). The acinar dilatation is chiefly attributed to increased viscosity of the pancreozymin-stimulated proteochylus with simultaneous decrease in secretin-induced secretion of fluid rich in bicarbonate. According to this hypothesis, the pancreatic acinous ectasia in azotaemia is the histomorphological manifestation of a so-called acinar dyschylia (Seifert, 1956; Becker, 1973). The following causative factors may be considered: direct toxic damage to the acinous epithelia by substances that are increased in azotaemia, such as guanidines; a dysregulation of the autonomic nervous system with a prevalence of the cholinergic, proteochylus-stimulating effects; and electrolyte disturbances. A decrease of secretin-liberation and thus a decreased secretion of hydrochylus has been thought to be responsible. Hypochlorhydria with a reaction in the upper duodenum above pH 4.5 might be a reason, because in azotaemia, hypoacidity has been described (Lieber & Lefèvre, 1959; Falcao et al, 1975), and has been attributed to neutralisation of the gastric acid by ammonia produced from urea by urease-producing bacteria. Above all the so-called uraemic gastroenteropathy has been thought to contribute to a secretin-deficit, especially when the secretin-producing endocrine cells in the duodenal mucosa are damaged in the course of an eventually erosive or ulcerative duodenitis (Boner & Berry, 1968).
Reasons in discussion:

Decrease of secretin-stimulated Hydrochylus by damage of secretin producing duodenal cells in "uroemic gastro-enteropathy", functional disturbance in Gastrin - HCl - Secretin - Hydrochylus - secretory-chain

Electrolytic disturbance with metabolic acidosis, imbalance of Ca\(^{++}\), K\(^{+}\)-ions, decrease of \(\text{+ HCO}_3\)

Disturbance of autonomous nervous system (prevalence of cholinergic stimulation)

Toxic damage of pancreatic acinar epithelia in acotaeemia

Figure 3. Pathological pancreatic changes in renal insufficiency

So-called uraemic enteroe-colitis has been recognised for nearly 150 years (for literature, see Castrup et al, 1970; Löhre et al, 1974; Löhre & Arnholdt, 1976). Mucosal lesions in azotaeemia may affect any level of the digestive tract from the mouth to the anus, manifesting themselves as oedema, bleeding and erosive or pseudomembranous or ulcerative inflammation (Figure 4). In a retrospective
investigation, performed together with Dr v Lüdinghausen, we found a description of macroscopic inflammatory lesions in 5% of 620 autopsy records of patients with clinically established azotaemia, who had died in the period 1961–1971.

Recently partial villous atrophy of small intestinal mucosa has been reported by Riecken and co-workers (Riecken et al, 1969; Riecken, 1970) in patients with renal insufficiency, who suffered from malabsorption (Bloch et al, 1973).

Vascular disturbances such as capillary thrombosis, arteriolonecrosis or haemorrhage were regarded as initiating factors of so-called uraemic enteropathy (Fischer, 1893; Würth, 1932; Jaffé & Laing, 1934; Matthieu & Roux, 1902). Nowadays, however, the changes in the intestinal mucosa are generally considered to be induced by toxic substances, secreted into the intestinal lumen (Löhrs et al, 1974), although the precise nature of these toxic substances is unknown.

Theoretically, a noxious agent could either affect the proliferating cells of the crypts or the mature absorptive cells on the surface of the villi. As is well known, in the intestinal mucosa of man and of the small laboratory animals the regenerative cell compartment is located in the lower two-thirds of the crypt. These proliferating cells go through a mitotic cycle with a mean duration of 10–14 hours in the small intestine, and of 20–25 hours in the large intestine of mice and rats, with a mean duration of the DNA-synthesis-phase of 6–8 hours. When migrating from the crypts to the villi the cells differentiate, acquiring the enzymic outfit for their absorptive role. In rats and mice the enterocytes migrate to the villous tips in about 48 hours, where they are shed into the lumen; in man the migration seems to last 3–6 days.
In order to establish whether and where the intestinal epithelium is affected by a noxious agent in azotaemia we have investigated the effects of experimental renal insufficiency on the intestinal epithelium in both rats and mice. We produced a short-term severe azotaemia in mice and chronic renal insufficiency in rats by 5/6 renal resection (Castrup et al, 1970; Löhrs et al, 1974; Löhrs & Arnholdt, 1976). In both experiments a significant prolongation of the mitotic

![Image](image_url)

**Figure 5. Changes in the generative cycle of intestinal crypt epithelium in experimental renal insufficiency**

162 mg% : mean urea i.s. : 120 mg% > 140 mg%
cycle of the regenerating crypt epithelia in small and large intestinal mucosa was observed (Figure 5). In short term renal insufficiency (r.i.) the total regeneration cycle was prolonged by up to 30% in the three small intestinal segments, and by up to 75% in large intestinal mucosa, compared with the controls. In chronic experimental r.i. the mitotic cycle time had increased by 14 to 40% in small intestine and by 43–54% in large intestine above the controls. There was a significant dependency on the degree of the r.i., estimated from the mean urea retention levels in serum. Since in man the most severe erosive and ulcerative mucosal lesions in azotaemia affect the large intestine, it is noteworthy that the most significant prolongation of mitotic cycle time in experimental r.i. occurs in the large intestine too.

The inhibition of normal epithelial cell regeneration as a consequence of a deceleration of the mitotic cycle led to a reduction of total mucosal thickness by up to 15%, and of the mean crypt cell number by up to 36% in the three small intestinal segments. Simultaneously histochemical analysis showed an unequivocal decrease of alkaline phosphatase activity in the epithelial brush border, regarded as a marker enzyme of enterocyte differentiation, in short term severe azotaemia. This result suggests interference with cell differentiation and was not encountered in chronic experimental r.i. where in contrast with short term azotaemia, there was an increase of the regenerative or the crypt cell population, respectively, with lengthening of the crypts. The increase of the regenerative cell population in the crypts seemed to compensate for the inhibition of the normal cell regeneration in this experimental model, because on histological examination there were no atrophic or erosive-ulcerative changes present in the intestinal mucosa.

From these results in experimental renal insufficiency, which I have briefly outlined, the following conclusions may be drawn: the noxious agent(s) in azotaemia seems to attack mainly the regenerating crypt epithelium. With sufficient time for adaptation, this inhibition can be compensated by enlargement of the crypt cell population.

From the studies in experimental renal insufficiency the following hypothesis for the genesis of uraemic enteropathy is suggested (Figure 6): when the inhibition of the physiological epithelial cell regeneration in renal insufficiency cannot be compensated by the mechanism described, for instance with the acute onset of severe azotaemia, inflammatory or erosive and ulcerative mucosal changes and/or a simple mucosal atrophy will occur. Immunological disturbances, as described in uraemia (Dobbelstein, 1975), may further promote inflammation. When there is time for compensatory changes, the crypt cell number and thereby the crypt size will increase. If decompensation occurs in this phase, not only erosive and ulcerative changes develop, but also the histological picture of lengthened crypts, similar to that seen in gluten-sensitive sprue, may result, as has been described in patients with chronic renal insufficiency (Riecken et al, 1969; Riecken, 1970). Such changes, perhaps in conjunction with disordered enterocyte matura-
Figure 6. Changes in small intestinal mucosa in uraemia: a possible and probably reversible sequence. A: short-term severe r.i. without compensation of impeded cell regeneration in uraemia. B: chronic r.i. with compensation of impeded cell regeneration in uraemia. C: decompensation due to intermittent increase of uraemia and/or additional injury.

tion, may be responsible for a malabsorption syndrome (Bloch et al, 1973). As possible reasons for decompensation of epithelial cell regeneration, azotaemic episodes or other factors must be taken into account, such as starvation (Wiebecke et al, 1969), cystostatic drugs (Eder & Löhns, 1965; Eder et al, 1966) or antibiotics (Eder & Goppelt, 1966).

Pathological changes in the pancreas and intestine which I have briefly tried to outline, are the morphological correlations of the severe complications in renal insufficiency. The assumption that they are induced by any dubious noxious agents characteristic of azotaemia, cannot be established from experiments alone. Fortunately, the experience of clinicians and pathologists suggests that the severe complications in the digestive tract in uraemia have been decreasing in recent years, perhaps as a result of improved management of renal insufficiency.

References

Baggenstoss, AH (1948) Archives of Pathology, 45, 463
Ball, WP, Baggenstoss, AH and Bargen, JA (1950) Archives of Pathology, 50, 347
Springer Verlag, Berlin, Heidelberg, New York
Bloch, R, Menge, H, Lange, H, Dombrowski, H and Riecken, EO (1973)
Zeitschrift für Gastroenterologie, 6, 535
Boner, G and Berry, EM (1968) Israel Journal of Medical Science, 4, 66

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Dobbeltstein, H (1975) *Klinische Wochenschrift*, 53, 461
Eder, M and Löhrs, U (1965) *Deutsches Archiv für klinische Medizin*, 210, 202
Fischer, J (1893) *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*, 134, 380
Jaffé, RH and Laing, DR (1934) *Archives of Internal Medicine*, 53, 851
Leynat, L (1933) *Mèse de Paris*
Lieber, CS and Lefèvre, A (1959) *Journal of Clinical Investigation*, 38, 1271
Matthieu, A and Roux, J (1902) *Archives générales de médecine*, 7, 14
Menten, ML and Kinsey, WC (1949) *Archives of Pathology*, 47, 90
Seifert, G (1956) *Die Pathologie des kindlichen Pankreas*. Thieme, Leipzig
Starzl, TE, Marchioro, TL, Rifkind, D, Holmes, JH, Rowlands, DT Jr and Waddell, WR (1964) *Surgery*, 56, 296
Stein, AA and Powers, SR (1956) *Archives of Pathology*, 62, 494
Wüth, W (1932) *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*, 284, 175

Open Discussion

DRUEKE (Paris) I want to ask Dr Löhrs if he has done similar studies on acutely or chronically starved animals and if there are similar observations on intestinal cell turnover or if it is quite different in those animals?

LOHRS We did experiments in starvation too, and what we found was not quite the same, but it was quite similar and to try to prevent the effects of starvation
in these experimental models, we gave the animals additional tube feeding and we did not find a decline in weight, so we think we can exclude starvation effects in these experiments.

HESCH (Hannover) I would like to come back to your first point concerning the pancreas. You were saying that perhaps secretin, or disturbed secretion of secretin, could be involved in what you were describing. It is very difficult to stimulate secretin under normal conditions. Do you know any data in which secretin has been measured in patients with renal failure and whether there is diminished secretion of secretin?

LOHRS I do not recall any evidence that there is a diminution. The arguments that this mechanism is involved are mostly derived from animal experiments and stimulation effects. Most of the illustration I showed is still hypothetical.

CHAIRMAN I think Dr Wizemann can speak about this question too.

WIZEMANN As an endocrinologist you know it is very difficult to measure secretin activity in the blood. As far as I know, there is no reliable test for secretin, so nobody could measure secretin activity in renal failure, and what Dr Lohrs said is a hypothesis derived from animal experiments.

HESCH Just briefly to comment that there are several very good, very sensitive assays for secretin — it is not a problem to measure secretin in the blood, but the only point is that you cannot stimulate it with anything. So the problem would be to find how to stimulate it in normals, and how to stimulate it in renal insufficiency and whether there is any difference.

CHAIRMAN Thank you Dr Hesch. Any more questions?

KOPP (Munich) I would like to ask a clinical question to Dr Lohrs, as to whether he could draw any conclusions from his experimental data regarding the clinical observation that the most frequent problem we see in uraemic patients is gastric bleeding.

LOHRS The same mechanism of inhibition of epithelial cell regeneration seems to occur in the stomach according to the work of, for instance, Gastrup and Lehnert, and in contrast to Wegener and his co-workers; but I think with the stomach another factor is the coagulopathy in uraemia. I think this is the main factor, that the surface epithelium is not regenerated in the way that it should be — and another point, the mucus on the surface has a changed quality, although the findings in this direction are equivocal.

CHAIRMAN I think that is the most important problem — the defence mechanism of the gastric mucosa is changed in the uraemic patient.

If there are no more questions, we will go on to the next two papers concerning the absorptive mechanisms in the small intestine. First we will hear Dr Grimmel; he is speaking about the absorption of organic substances, and then we will hear Dr Hesch speaking about the problems of absorption of inorganic substances, e.g. calcium.