Virchows Arch [Pathol Anat] (1986) 409:105–117

Virchows Archiv A

The gastric juice aspiration syndrome (Mendelson syndrome)

Aspects of pathogenesis and treatment in the pig*

H. Popper[1], **F. Juettner, and J. Pinter**
Pathologisches Institut der Universität Graz, Auenbruggerplatz 25, A-8036 Graz, Austria

Summary. The gastric juice aspiration syndrome (GJA-S, Mendelson syndrome) was studied experimentally in pigs. Following instillation of gastric juice into the right main bronchus necrosis of pneumocytes and bronchiolar epithelium occurred with activation of complement and a prostaglandin E releasing system (possibly the kinin system). Cell necrosis was followed by loss of surfactant and formation of hyaline membranes, rich in immunoglobulin M. The alveolar damage organized, resulting in intraalveolar and interstitial fibrosis.

The causative agents were found to be both gastric hydrochloric acid and pepsin. Pretreatment with H_2-, or acetylcholin-receptor-antagonists (cimetidine or pirenzepin) as well as buffering of the gastric juice to a neutral pH did not prevent lung fibrosis. If a mixture of aluminium hydroxide, magnesium carbonate and oxethazaine was added to the aspirate, development of lung fibrosis was prevented, but severe granulomatous reaction with foreign body giant cells within both lungs evolved. Kallikrein inhibitor, when administered intravenously not later than 3 min after artificial aspiration, protected the left lung completely and large areas of the right. If infused within 60–90 s complete protection of the left lung and the right upper lobe was achieved. In the majority of the animals a mild focal fibrosis developed in the right lower lobe; in one experiment both lungs were devoid of fibrotic areas. If Kallikrein inhibitor was infused 5 min prior to aspiration, lung fibrosis was not prevented.

Key words: Gastric juice aspiration – Lung fibrosis – Complement activation – Kallikrein inhibitor

* Parts of this investigation were presented at the 9th European Congress of Pathology, Hamburg, 19.–24.9.1983, the Anual meeting of the Austrian Society of Pulmonary diseases and tuberculosis, Linz, 12.–15.5.1983, and at the congress of the European Society for clinical Investigation, Milan, March 1984

Offprint requests to: H. Popper at the above address

Introduction

1946 Mendelson described the clinical and pathological features of gastric juice aspiration (GJA-S) following obstetric anesthesia. Although many other reports followed (see reviews of Burkhardt and Gebbers 1983 and Hasleton 1983), the aetiology and the morphological course remained speculative. Some authors demonstrated the significance of pH experimentally by administration of boiled gastric juice, producing the same X-ray results as with native gastric juice (Bosomworth and Hamelberg 1962). Other investigators found improvement following administration of Cimetidine, which is known to influence gastric acid secretion (Berquist et al. 1980). The therapeutic use of cimetidine is based on a theoretical benefit of pH-elevation only.

How is it possible that such small amounts of gastric juice aspirated during general anesthesia and diluted by the bronchial and lung fluid should cause such severe fibrosis of the lung, sometimes causing death of the patient. Why is antacid therapy prior to surgery sometimes without effect? (Whittington et al. 1979). Which mechanism causes total fibrosis of both lungs step by step in a period of only 4 weeks? (Ratzenhofer et al., in preparation). To answer these questions we developed an experimental model. It has been suggested that a pH lower than 2.0 might be the causative agent of GJA-S. However, we failed to produce a classic GJA-S in rabbits or guinea pigs using their own gastric juice although the latter produce a gastric juice with a pH range from 1.1 to 2.5. Therefore we tried pigs, known to have a similar gastric enzyme content to human beings.

Methods

After i.m. premedication by a muscle relaxant, miniature pigs of either sex with a body-weight from 20.5 to 100 kg were anaesthesized using halothane (0,8 Vol %) and dinitrogen oxide (2 l/min). Gastric juice was obtained from each animal by gastric tube, and filtered through fine-meshed gauze. pH was determined by a Schott digital pH-meter.

Surgical procedure. Through a tracheotomy, performed under aseptic conditions, a fiberbronchoscope was inserted into the tracheobronchial tree. Fiveteen to twenty-four ml of gastric juice were instilled into the right main bronchus without applying pressure. Then both the tracheostomy and the skin were closed. Artificial ventilation with oxygen was continued until onset of spontaneous respiration.

Preparation of histological specimens. The animals were killed one hour and 1, 2, 3, 6 or 15 days after instillation of gastric juice. The trachea and both lungs were removed en bloc. 10% neutral formaldehyde solution was instillated into the trachea from a bottle standing 50 cm above the lungs. After being filled with formaldehyde until the pleural surfaces were smooth, the lungs were transferred into a bath of 10% neutral formaldehyde. At least 8 histological specimens per lobe were taken from areas macroscopically suspicious for fibrosis, and processed for routine histology. The sections were stained with haematoxylin eosin (HE), trichrome according to Masson (TRI), Periodic acid Schiff reaction (PAS), Elastica van Gieson (EG) and Gomori's silver impregnation (Gom). The peroxidase activity of granulocytes and macrophages was investigated by the DAB-method and the method by Tice and Woolman (1972), using fixed and unfixed sections.

Immunohistochemistry. Unfixed cryocut sections and formaldehyde-fixed frozen sections were incubated with the following antibodies: sheep-anti-swine-IgA, rabbit-anti-swine-IgM, rabbit-anti-swine-IgG, rabbit-anti-swine-complement C3c, diluted 1:50 or 1:100, (Nordic Immun. Lab., Tilburg) and anti-prostaglandin E2 produced in rabbit (by the carbodiimide coupling method, Pescar and Herting 1973) diluted 1:300; second antibodies against sheep IgG and rabbit IgG coupled with FITC were diluted 1:20 or 1:30 (Nordic Immun. Lab., Tilburg). Formaldehyd fixed frozen sections were pretreated with pronase (1%) for 30 min prior to immunoreaction. The reaction was stopped by ice cold TRIS-Saline puffer, pH 7.4. Controls were done by preabsorption of the antisera with the antigen (prostaglandin E2, normal swine serum) or zymosan activated normal swine serum (for anti-complement absorption) and by omitting the primary antibody. Photographs were done with a Leitz Dialux 20 microscope equipped with a Vario-Orthomat.

Electronmicroscopy. Small sections from macroscopically identified fibrotic areas were fixed in 3% glutaraldehyde in 0.1 M Cacodylate buffer, pH 7.5 for 3 h.

In one experiment longitudinal sternotomy was performed one hour after GJA. The right pulmonary artery and veins were dissected and cannulated. The lung was perfused with physiological saline (37° C) until almost clear fluid returned from the pulmonary veins. Thereafter the lung was perfused with 3% glutaraldehyde. The right lung was removed then and put into 3% glutaraldehyde for three hours. Immediately after pneumectomy the animal was killed and the left lung was cut off. Some parts were frozen in isopentane (cooled in liquid nitrogen) and processed for immunofluorescence, others were processed for electron microscopy.

After fixation, sections from these both lungs as well as glutaraldehyd fixed sections from lungs of the other experiments were rinsed with 0.1 M cacodylate buffer for two days. The sections were postfixed and contrasted in 1% Osmium tetroxide solution, dehydrated in ethanol and embedded in Epon 812. Semithin sections were stained with a mixture of alkoholic toluidine blue and azur blue. Ultrathin sections were cut using a Reichert OM-U2. The latter were examined with a Philips EM 400 electron microscope.

Control group. One pig was sacrificed 1 h after GJA (No. 17) 2 at the 1st day (No. 1, 35) 2 at the 2nd day (No. 37, 38), 2 at the 3rd day (No. 39, 40), 3 at the 6th day (No. 2, 3, 41) and 2 at 15 days after GJA (No. 4, 36). In these animals GJA was caused with autologous filtered GJ previously obtained, and the "native" morphological sequence was studied.

Evaluation of fibrosis. In all cases fibrosis was measured and partly quantified in the following way: the percentage of fibrotic to non fibrotic areas was assesed from every histological section and a mean percentage was set up for every case. Fibrotic areas of more than 60% of total sectioned lung areas were classified as 3+ including all autopsy cases. 30–60% fibrotic areas were classified as 2+ and below 30% as 1+.

Experimental procedure for clarifying Aetiology (Table 1). Two pigs were given 20 ml 0.1 HCl instead of gastric juice (pH 0.7); 2 aspirated 2 g pepsin (OEAB 9) dissolved in 20 ml distilled pyrogen free water (pH 4.6). Another was given 2 g pepsin dissolved in distillated water, the pH being adjusted to 2.9 with 3 ml 0.1 N HCl. In one experiment 2 g pepsin was dissolved in 7 ml H_2O and 3 ml 0.1 N HCl. After an incubation period of 3 min at 22° C this solution was buffered with 0.1 NaOH to pH 7. All pigs were sacrifized after 6 days. Prior to administration, the gastric juice of four animals was buffered with sterile $NaHCO_3$ to a pH of 5 or 7 respectively. This latter group was placed in both tables, because $NaHCO_3$ on one hand might have therapeutic effects (neutralization of HCl) and on the other might add some data to the solution of the question of whether gastric enzymes or HCl alone is the main aetiologic agent of GJA-S.

Experimental therapy (Table 2). Four pigs were treated with Cimetidine orally (3 animals for 28 days with 2×400 mg/day, one for 28 days with 4×400 mg/day). Four were given Pirenzepine (3 animals for 8 days with 2×50 mg orally and one for 3 days with 3×20 mg intramusculary daily) prior to artifical GJA. In another experiment 3 were given kallikrein inhibitor (500000 I.U.) as bolus injection into the internal jugular vein, 2 or 3 min after

Table 1. Hydrochloric acid versus enzyme pepsin – the search for the causative agent. All pigs were sacrificed 6 days after aspiration and the lungs examined for developed fibrosis. The degree of fibrosis in autopsy cases were assessed as + + + on a three grade scale. The extension of fibrosis in all lobes and the occlusion of alveolar lumina were estimated and compared

sw. Nr.	Gastric juice or analogs	pH	Aspirated ml/kg body	Fibrosis of the	
				right lung	left lung
23, 24	0,1 N HCl	0,75	0,95/m 0,66 ml	+ +	+ +
25	2 g pepsin dissolved in 20 ml H_2O	4,6	0,25 ml	+ + +	+ + − + + +
26	2 g pepsin + 3 ml 0,1 N HCl + H_2O ad 20 ml final volume	2,9	0,36 ml	+ +	+
27	2 g pepsin + 3 ml 0,1 N HCl + 7 ml H_2O 3 min + 0,1 N NaOH + H_2O ad 20 ml	2,98 ↓ 7,05	0,28 ml	+	+
6, 7	gastric juice buffered with $NaHCO_3$	5,0	0,56/0,69 ml	+ +	+ +
5, 8	gastric juice buffered with $NaHCO_3$	7,0	0,55/0,7 ml	+ +	+ − + +

experimental GJA. One swine received kallikrein inhibitor (1 Million I.U.) 4 min after aspiration (No. 20, not shown in the table), in 4 swines kallikrein inhibitor (1 Million I.U.) was injected 60 and 90 s after GJA.

Two pigs were pretreated with 1 million units kallikrein inhibitor 5 min before GJA.

In 2 animals an antacid drug (Tepilta^R) containing aluminium hydroxide, magnesium carbonate and Oxethazaine, was mixed to filtered GJ prior to artificial aspiration.

Results

The pathogenesis of GJA-S. The pathological changes of early GJA-S were characterized macroscopically and microscopically by haemorrhages and oedema. Microscopically necroses of pneumocytes (mainly type II (Fig. 1 a, b)) and bronchiolar epithelial cells, expecially the ciliated ones were most prominent within the first hour (Fig. 2). Later necroses of type I pneumocytes, Clara cells and goblet cells also occurred. Within one hour neutrophilic granulocytes infiltrated the lung tissue (Fig. 3). No peroxidase activity was demonstrable histochemically in neutrophils or in macrophages, possibly indicating release of enzyme(s) with peroxidase-like activity. In and around macrophages complement component C3c was found. Prostaglandins of E-type were detected within pneumocytes in the alveolar lumina, in septa (Fig. 4), and sometimes also within the endothelium of small blood vessels. From the third day on macrophages prevailed among the inflammatory cells, although bronchiolar and alveolar necroses were still present. Desintegrated elastic fibers were found in many areas. No stretched or

Table 2. Treatment of GJA-S by different drugs. The pigs were sacrificed 6 days after GJA. Lung fibrosis was compared with fibrosis in autopsy cases, the later taken as + + +

sw. Nr.	Treatment, pretreatment	ml aspir. per kg body wgh.	Fibrosis in the			
			r. up. lobe	r. lo. lobe	l. up. lobe	l. lo. lobe
5, 6, 7, 8	gastric juice buffered with $NaHCO_3$ to pH 5 or 7	0,55–0,7 ml	+ to + +	+ +	+	+ to + +
13, 14, 15, 18	Cimetidine administered for 4 weeks in a low dose 800 mg/day	0,22–0,4 ml	+ +	+ + +	+	+ +
	in a high dose 1,600 mg/day		+	+ +	+	+
9, 10, 16, 19	Pirenzepine administered for 8 days perorally 100 mg/day	0,2 –0,4	+ +	+ + +	+	+ +
	for 3 days intra-muscullary 60 mg		+ +	+ + +	+	+ +
11, 12, 21	i.v. injection of Kallikrein inhibitor 2–3 min after aspiration (500,000 IU)	0,27–0,45 ml	– to (+)	+ +	–	–
22, 28, 29, 30	i.v. injection of 1 Mill units of Kallikrein inhibitor 60–90 sec after aspiration	0,25 ml	–	– to +	–	–
31, 32	i.v. injection of 1 Mill units of Kallikrein inhibitor 5 min prior to GJA	0,25–0,34	– to + +	+ + to + + +	–	– to + +
33, 34	GJ combined with oxethazine, $MgCO_3$ and $Al(OH)_3$ (final pH 7,4/7,67)	0,31–0,33	– to + + foreign body react.	+ + + foreign body react.	– to + foreign body react.	– to + foreign body react.

lamellated surfactant was found by electron microscopy in most areas, hyaline membranes being present in these regions. Within the hyaline membranes immunoglobulins of the M-type were found.

Between days 2 and 6 reticulin fibers were formed intraalveolarly and interstitially. Necroses were organized by fibroblasts and myofibroblasts. Some macrophages were found to bridge from one side of an alveolus to the other (Fig. 5). Finally collagen fibers formed scars, covered by pneumocytes, which were situated in part in an intra-alveolar position and in part interstitially (Fig. 5). In contrast to organizing pneumonia no proliferation of capillaries and no granulation tissue was found.

Aetiology. In all 9 pigs of this group (Table 1) the pulmonary lobes were examined for the development of fibrosis, which was demonstrable 6 days

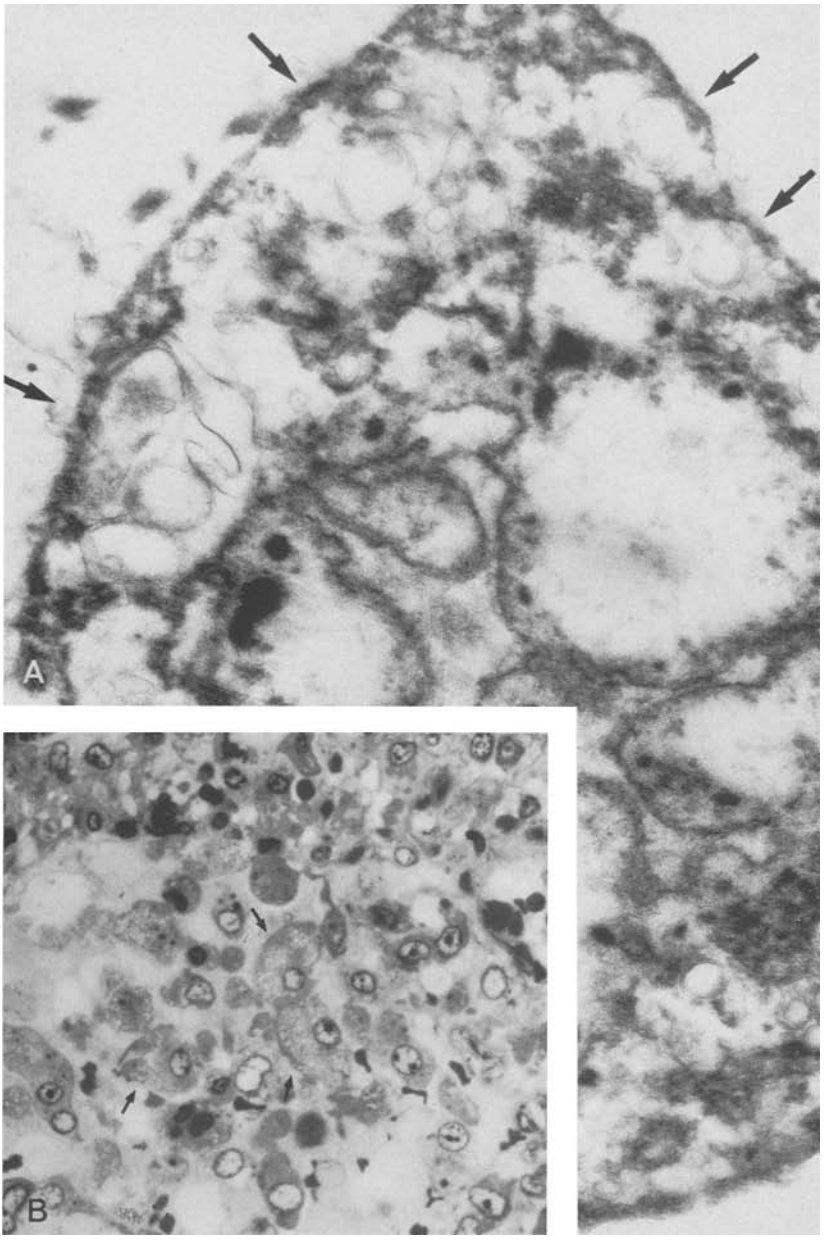


Fig. 1. a Necrosis of a pneumocyte type II. Remnants of lamellar bodies are a marker for cell type (*arrows*). Electron microscopy, ×4,000. **b** *Inset*. Many desquamated pneumocytes are seen within 1 h, showing vacuolar degeneration (*arrows*). HE ×320

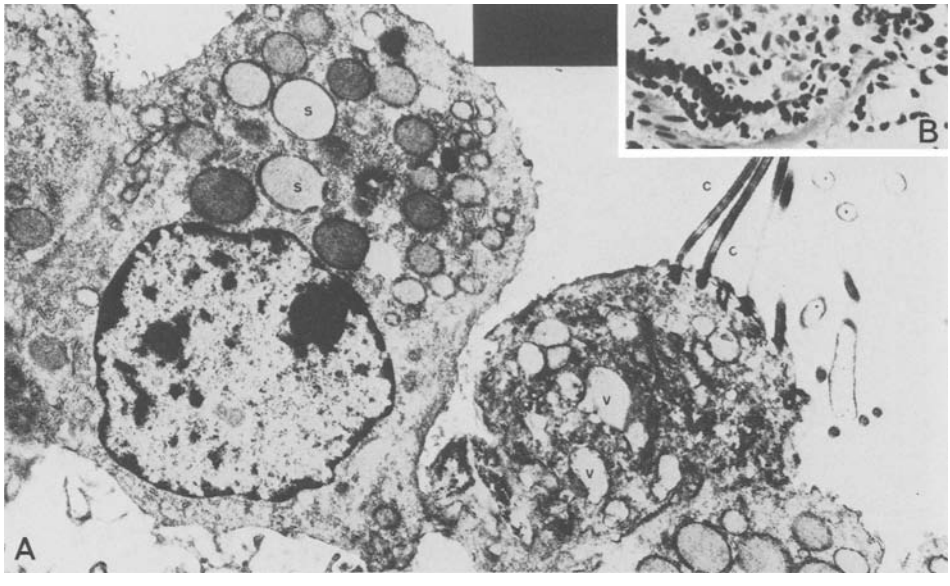


Fig. 2. a Electron microscopy of a Clara cell and a ciliated cell. Note the loss of tight junctions between the two cells, the loss of cilia and the vacuolar degeneration of the ciliated cell. IT = intact tight junction, *V* = vacuoles, *C* = cilia, *S* = secretory granules. × 2,400. **b** *Inset*. Terminal bronchiolus. In the lumen many desquamated epithelial cells are seen. The epithelial layer exhibit a red granular cytoplasmic reaction with the trichrome stain, × 360

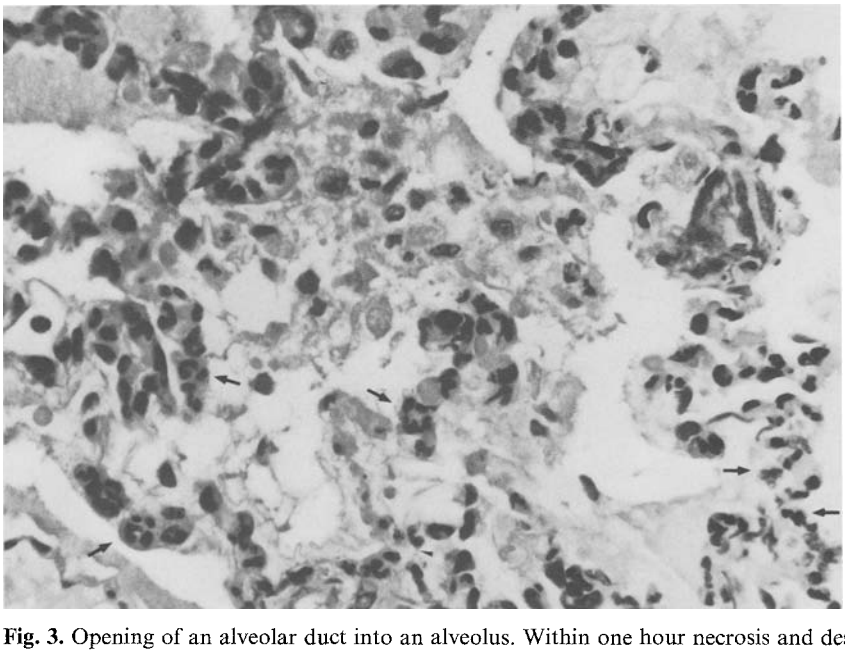


Fig. 3. Opening of an alveolar duct into an alveolus. Within one hour necrosis and desquamation of epithelial cells, infiltration of neutrophils (*arrows*) and oedema occurr. The elastic fibers at this time are mostly intact. EG, × 360

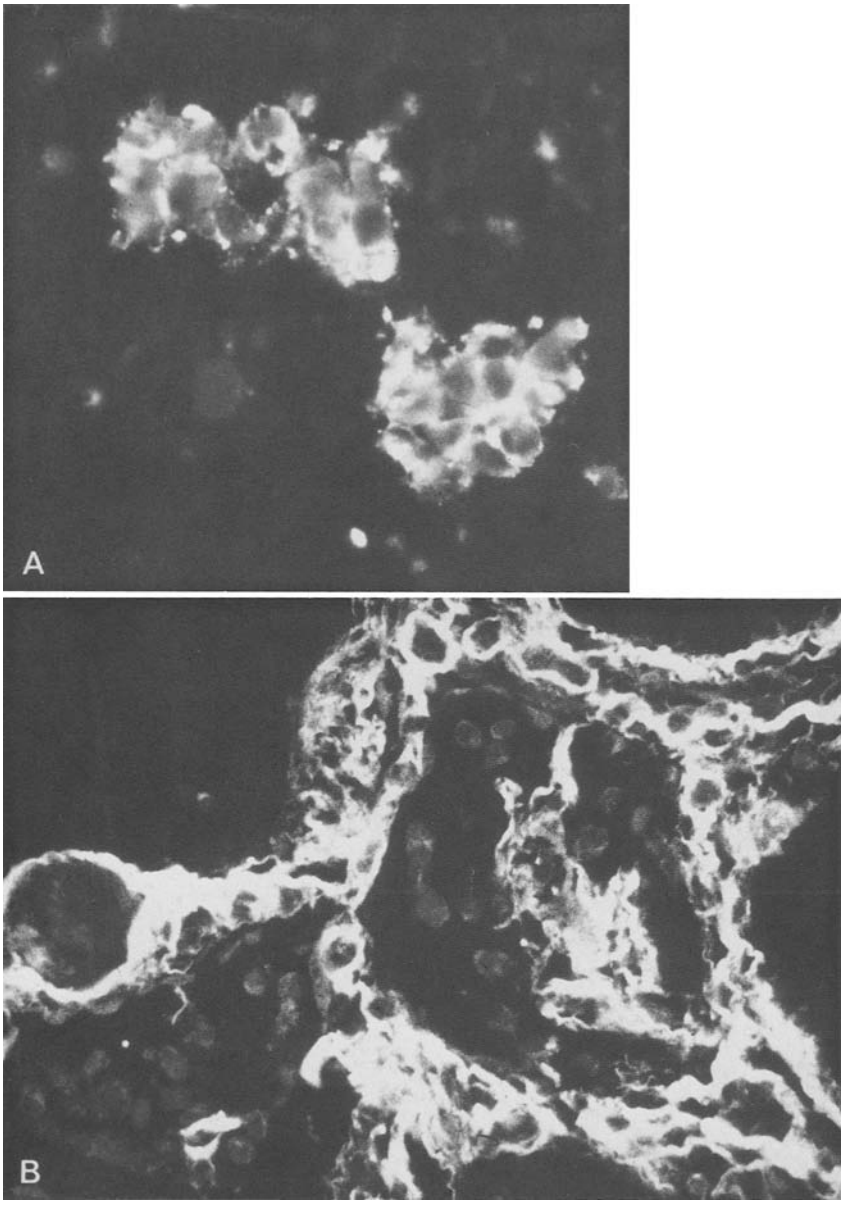
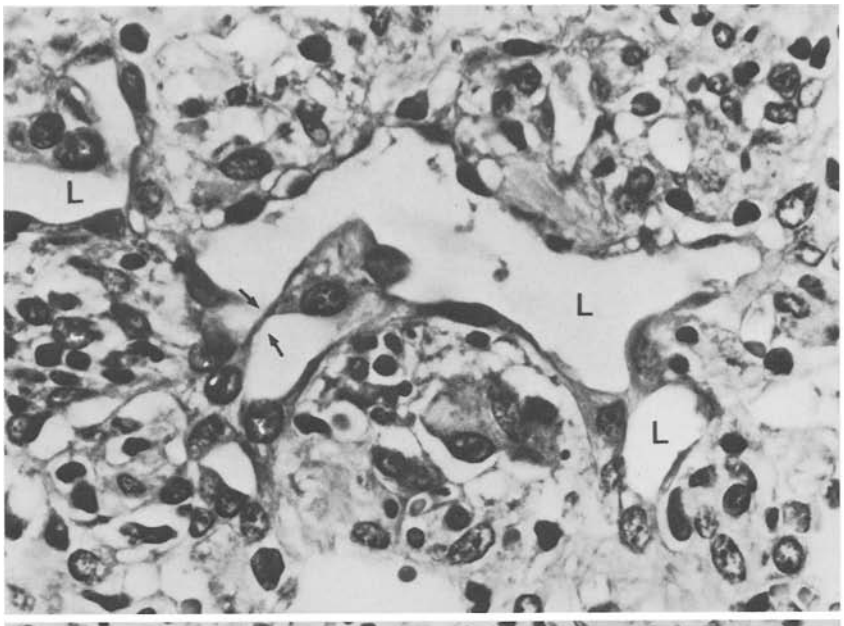
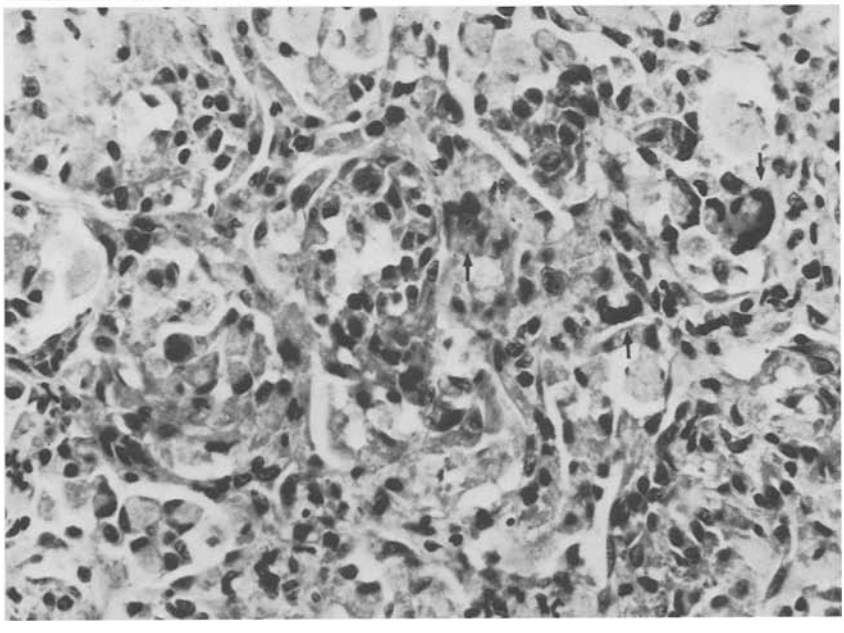


Fig. 4. Demonstration of prostaglandin E on alveolar macrophages and pneumocytes within early necrosis **a** and in endothelial cells and within pneumocytic necrosis **b**. Rabbit antibodies against synthetic prostaglandin E_2, indirect immunofluorescence. ×250

after GJA in the control experiments. The buffering of GJ, even to neutral pH, did not prevent the development of lung fibrosis in the right and left lung. Hydrochloric acid or pepsin, alone or in combination caused lung fibrosis. So did pepsin and hydrochloric acid buffered with sodium hydroxide to neutral pH (Table 1).



5



6

Fig. 5. Intraalveolar and interstitial fibrosis of the lung – some remaining alveolar clefts (*L*). The fibrotic areas are covered by pneumocytes, macrophages, fibroblasts and myofibroblasts, which sometimes show a bridging of two opposite sides of the remaining alveolus (*arrows*). HE, × 500

Fig. 6. Severe foreign body reaction as a consequence of the aspiration of gastric juice buffered with Aluminium hydroxide, Magnesium carbonate and Oxethazaine. Many foreign body and Langhans giant cells are seen (*arrows*). HE, × 225

Therapy. Pirenzepine (a muscarinic anticholinergic drug) and Cimetidine (a H_2-receptor-antagonist), neither prevented necroses of pneumocytes and bronchiolar epithelial cells nor subsequent lung fibrosis. The only effect demonstrable was a slightly reduced number of microscopically visible fibrotic areas after high-dosage – Cimetidine (Table 2). Kallikrein inhibitor, if injected 2–3 min after GJA completely prevented lung fibrosis in the left lung and in most parts of the right upper lobe, whereas in the right lower lobe numerous fibrotic areas were found (Table 2). If the kallikrein inhibitor was injected 4 min after aspiration, fibrosis developed in most parts of the right upper lobe and in some areas of the left lung, especially in alveolar subsegments near the left hilus.

Injections of kallikrein inhibitor within 60–90 s after GJA prevent the development of lung fibrosis in the left lung and the right upper lobe and only mild focal fibrosis occurred in the right lower lobe. In one of the 4 experiments both lungs were completely protected by the kallikrein inhibitor.

When kallikrein inhibitor was injected 5 min prior to GJA, severe fibrosis was found only in the right lower lobe of the first and in 3 lobes of the second animal (Table 2).

The mixture of Al (OH_3), $MgCO_3$ and Oxethazaine prevented lung fibrosis, but instead of it, severe granulomatous foreign body reaction developed in the right lower lobe. (Table 2, Fig. 6).

Discussion

From our results we are able to answer some of the questions which have been under discussion for the last 3 decades. The agents which cause the GJA-S are hydrochloric acid as well as the enzyme pepsin. The latter causes a higher degree of lung damage and fibrosis than HCl alone. This is demonstrated by pepsin aspiration and by neutralisation of the gastric juice hydrochloric acid. All previous investigators (Mendelson 1946; Teabeaut 1952; Hamelberg and Bosomworth 1964; Vandam 1965) dealing with this questions inactivated the gastric juice enzymes and were able to produce a GJA-S and thus concluded that HCl was the causative agent. Non of them tested the GJAS potency of gastric enzymes, expecially pepsin.

Teabeaut (1952) raised some doubts about the potency of GJ to induce lung fibrosis. In our experiments we were able to produce lung fibrosis with aspirated GJ independently of pH (ranging from 0.7, HCl alone, to 7.0, GJ buffered with $NaHCO_3$) agreeing with the findings of Schwartz et al. (1980).

Moreover, from our investigation we were able to elucidate a sequence of events in the pathogenesis of the GJA-S. The initial event is necrosis of pneumocytes and bronchiolar epithelial cells. The early predominance of necrotic type II pneumocytes might be due to an initial uptake of GJ by these cells followed by their death. Nerosis of type I pneumocytes occurs within the first day (as found by Salley et al. 1979). Concomitantly the complement cascade was activated and arachidonic acid was cleaved. Com-

plement components might be cleaved from circulating precursor molecules present within the early oedema fluid and activated by the pneumocytes II as has been demonstrated for monocytes/macrophages (Brade and Bentley 1980). Arachidonic acid is cleaved from the phospholipids of the cell membranes by the action of phospholipase A2. This release can be induced by kinins, i.e. bradykinin (Lembeck et al. 1976; Juan 1977) but possibly by complement components as well (as assumed by Ogawa et al. 1981). Once arachidonic acid is cleaved from the phospholipids it is metabolized to prostaglandins and thromboxanes via cycloxygenase and to leukotrienes by the lipoxygenase pathway (Goetzl 1980). We were able to demonstrate one of these products, PGE in the early pneumocyte necroses and in endothelial cells of the vascular bed. All these substances act as vasodilators, chemotaxins or bronchoconstrictors (Goetzl 1980; Higgs et al. 1979) and might be responsible for the early alveolar oedema, haemorrhage and granulocytic infiltration (Salley et al. 1979; Glauser et al. 1979; Stothert et al. 1981). The negative reaction for myeloperoxidase in granulocytes and macrophages is another interesting finding. It could be interpreted as a consequence of peroxidase release or consumption by processes in which granulocytes and macrophages are involved.

The formation of hyaline membranes may be explained by deficient metabolism of the surfactant induced by necrosis of pneumocytes. The presence of immunoglobulin M within the hyaline membranes might be oedema-associated or a sign of the early inflammatory reaction.

The change in inflammatory cell proportions in the lesion occurs between the first and the third day. Macrophages are the predominant inflammatory cell population in newly formed and older necroses. The macrophages, and later, proliferating fibroblasts and myofibroblasts from the alveolar walls, start to organize the areas of necrosis. Fine reticulin fibers and later collagen bundles appear. Finally alveoli are filled by scar tissue and only small clefts covered by regenerated pneumocytes remain, sometimes associated with bronchiolar metaplasia. In contrast to the alveolar process the regeneration of bronchiolar epithelial cells results in complete restitution.

In contrast to the findings in man, lung damage in the pig seems to be self limiting. In our animals killed after 15 days, no new necrosis was seen in contrast to our autopsy cases. At the present time we cannot explain this discrepancy.

We are well aware that all these morphological events and sequences are by no means specific or even pathognomonic for GJA-S. But they are a common mechanism by which the lung parenchyma reacts when exposed to a variety of stimuli (Hasleton 1983; Burghardt and Gebbers 1983; Fukuda et al. 1985; Mitsuhashi et al. 1985).

On the basis of these pathogenetic considerations some of our therapeutic results are not surprising. As the pH-value is of little importance for development of GJAS, drugs which reduce or inhibit hydrochloric acid secretion or simply elevate the pH are of little effect on the formation of lung fibrosis.

We expected the beneficial effect of kallikrein inhibitor, because of in-

volvement of arachidonic acid metabolites and complement in the initial mechanism of alveolar damage. But we are still surprised by the degree of reduced fibrosis. The effect of kallikrein inhibitor is an indicator "ex juvantibus" that kininogen metabolites might be involved into the GJA-caused lung damage. The formation of small focal fibrotic areas in the lower right lobe, the site of first contact of GJ to lung parenchyma might be due to direct "toxic" initial damage by concentrated gastric juice. It is known that aspirated fluid spreads to the lung periphery within 12–18 s. (Hamelberg and Bosomworth 1964). Therefore gastric juice, placed in the right main bronchus and spreading mainly into the lower lobe under our experimental conditions, can cause initial lung damage until GJ action is limited by the kallikrein inhibitor. When the inhibitor is injected prior to GJA, however, fibrosis is not prevented. Possibly kallikrein inhibitor itself is inactivated and/or metabolized within these 5 min.

The therapy with an antacid drug combination containing $Al(OH)_3$, $MgCO_3$ and Oxethazaine prevented lung fibrosis but created severe granulomatous lesions with numerous foreign body giant cells, resulting in a reduction of alveolar surface suitable for gas exchange. Kallikrein inhibitor seems to interfere with the initial pathogenetic mechanisms, otherwise triggering the alveolar damage which ends up in irreversible fibrosis. An initial inhibition of the pathogenetic events by kallikrein-inhibitor however only seems to be possible if the drug is administered within 2–3 min after aspiration. Further studies are necessary to see whether kallikrein-inhibitor may be recomended for this indication in clinical use.

Acknowledgement. The authors wish to thank Mrs. R. Steiner and D. Langhart for their skillfull histological assistence, Mr. I. Georgiev for the fotoprints and Mrs. H. Schleich for typewriting the manuscript. One half of our miniature swines were a generous gift by Bayer-Pharma, Austria. H. Popper is a recipient of a grant from the Oesterr. Fonds zur Förderung der wissenschaftlichen Forschung (Projekt No P 4974) which is gratefully acknowledged.

Addendum: kallikrein-inhibitor therapy has been successfully applied in 4 cases of human GJA-S.

References

Berquist WE, Rachelefsky GS, Kadden M, Siegel SC, Katz RM, Fonkalsrud EW, Ament ME (1981) Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children. Pediatrics 68:29–35

Bosomworth PP, Hamelberg W (1962) Etiologic and therapeutic aspects of aspiration pneumonitis. Experimental study. Surg Forum 13:158–159

Brade V, Bentley C (1980) Synthesis and release of complement components by macrophages. In: Mononuclear phagocytes, part II, van Furth R (ed) Martinus Nijhoff Publ., The Hague-Boston-London, pp 1385–1413

Burghardt A, Gebbers JO (1983) Pathogenetisch komplexe Lungenerkrankungen. In: Doerr W, Seifert G, Uehlinger E (Hrsg) Spezielle Pathologische Anatomie, Bd. 16/II, Pathologie der Lunge, Springer, Berlin Heidelberg New York Tokyo, pp 809–986

Fukuda U, Ferrans VJ, Schoenberger CI, Rennard StI, Crystal RG (1985) Patterns of pulmonary structural remodeling after experimental paraquat toxicity. Am J Pathol 118:452–475

Glauser FL, Millen JE, Falls R (1979) Increased alveolar epithelial permeability with acid aspiration: The effects of high-dose steroids. Am Rev Resp Dis 120:1119–1123

Goetzl EJ (1980) Mediators of immediate hypersensitivity derived from arachidonic acid. N Engl J Med 303:822–825
Hamelberg W, Bosomworth PP (1964) Aspiration pneumonitis, experimental studies and clinical observations. Anesth Analg (Cleve) 43:669–677
Hasleton PS (1983) Adult respiratory distress syndrome – a review. Histopathology 7:307–332
Higgs GA, Moncada S, Vane JR (1979) The role of arachidonic acid metabolites in inflammation. In: Weissmann G, Samuelsson B, Paoletti R (eds) Advances in inflammation research, vol. 1, Raven Press, New York, pp 413–418
Juan H (1977) Mechanism of action of bradykinin-induced release of prostaglandin E. Naunyn-Schmiedeberg's Arch Pharmacol 300:77–85
Lembeck F, Popper H, Juan H (1976) Release of prostaglandins by bradykinin as an intrinsic mechanism of its algesic effect. Naunyn-Schmiedeberg's Arch. Pharmacol 294:69–73
Mendelson CL (1946) The aspiration of stomach contents into the lungs during obstretic anesthesia. Am J Obst Gynecol 52:191–203
Mitsuhashi T, Shimazaki M, Chanoki Y, Kuwahara H, Sakai T, Masuda H (1985) Experimental pulmonary fibrosis induced by trisodium citrate and acid-citrate-dextrose. Exp Mol Pathol 42:261–270
Ogawa H, Kunkel SL, Fantone JC, Ward PA (1981) Digestion of the fifth component of complement by eosinophil lysosomal enzymes. Virchows Arch [Cell Pathol] 38:149–157
Pescar B, Herting G (1973) Release of prostaglandins from isolated cat spleen by angiotensin and vasopressin. Naunyn-Schmiedeberg's Arch Pharmacol 279:227–234
Salley S, Santo GV, Barnhart MI (1979) Immediate histopathology of hydrochloric acid aspiration. Scan Electron Microsc 3:911–920
Schwartz DJ, Wynne JW, Gibbs ChP, Hood CI, Kuck EJ (1980) The pulmonary consequences of aspiration of gastric contents at pH values greater than 2.5. Am Rev Resp Dis 121:119–126
Stothert JC, Weaver LJ, Carrico CJ (1981) Lung albumin content after acid aspiration pulmonary injury. J Surg Res 30:256–261
Teabeaut JR (1952) Aspiration of gastric contents. An experimental study. Am J Pathol 28:51–67
Tice LW, Wollmann SH (1972) Ultrastructural localization of peroxidase activity in some membranes of the typical thyroid epithelial cell. Lab Invest 26:63
Vandam LD (1965) Aspiration of gastric contents in the operative period. New Engl J Med 273:1206–1208
Whittington RM, Robinson JS, Thompson JM (1979) Fatal aspiration syndrome despite antacids and cricoid pressure. Lancet 48:228–230

Accepted December 30, 1985