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Chapter 11

Discussion

Gyula Mozsik and Imre Szabó

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http://dx.doi.org/10.5772/60105

In the discussion, we will focus our attention on different main points of our present work:

11.1. Etiological and terminological problems of gastrointestinal mucosa (ulcers in humans);

11.2. Clinical pharmacology;

11.3. Biochemical results of the human gastrointestinal tract;

11.4. Results of biochemical–pharmacological studies in animal experiments;

11.5. Direct cellular damaging effects of ethanol, indomethacin and *Helicobacter pylori* on freshly isolated rat gastric mucosal cells;

11.6. Observations with stable cell lines;

11.7. General conclusions;

11.8. Present and future observations.

11.1. Etiological and terminological problems of gastrointestinal mucosa damage (ulcers in humans)

The developmental mechanisms of the acute (dominantly in experimental models) and chronic antral, duodenal and jejunal ulcers are unknown. Before the use of the term "gastroduodenal ulcer" – without any recognition of the causative factor(s) – we used the term "genuine ulcer" "(in about 80% of total number of patients with GI ulcer).

After the publications of Waren and Marshall (1983) and Marshall and Waren (1983), most gastroenterologists accepted the presence of *Helicobacter pylori* as the real cause of PUD – an infectious disease; however, some experts are of the opinion that the presence of *Helicobacter pylori* is only one of the different causative factors (hyperacidity, physical and chemical stress, drugs, psychical status, trauma, different diseases of central nervous system, etc.). These

problems of the etiological role of *Helicobacter pylori* in peptic ulcer disease have been reviewed very recently [Buzas Gy. (Ed.) *Helicobacter pylori*: a Worldwide Perspective 2013. Bentham Science Publishers. Sharjah, UAE – Oak Park, IL, USA]. The overall role of *Helicobacter pylori* infection in peptic ulcer disease has been emphasized after Barry James Marshall and John Robin Warren (Royal Perth Hospital, Australia) received the Nobel Prize. The experimental approach to ulcer development and prevention was based on different physiological, pathological and pharmacological fields (with the exception of experimental observations with Mogolian gerbils which is sensitive to *Helicobacter pylori* infection) (Takahashi et al., 1998). Hence, there is a contradiction between the etiologies of human gastric and duodenal ulcers and experimental ulcers in animals.

Changes in the suggested etiological factors of ulcer diseases appeared in the actual levels of applied drugs in the medical treatment of peptic ulcer patients (parasympatholytics, antacid compounds, histamine$_2$ receptor blockings, antigastrin compounds, proton pump inhibitors and the eradication treatment since 1980s).

It is important to clarify that the "classical histological definition of peptic ulcer diseases" is given by the presence of gastrointestinal mucosal damage which can be histologically characterized as a mucosal defect reaching the muscularis mucosae.

The term "secondary ulcer" was introduced as peptic ulcer disease associated with stress, burn, chronic liver, kidney and pulmonary diseases (in about 20% of patients with GI ulcer).

The connotation and use of the term PUD changed significantly in the past decade, when NSAID-induced gastrointestinal mucosal injury was found to be the cause of GI bleedings (ulcers) in patients in everyday medical practice. A couple of years ago, the term "non-ulcer disease" (NUD) was published by Scandinavian researchers, which indicated clinically the same symptoms as active peptic ulcer, however, without any endoscopic and histologic features.

Earlier it was thought that the primary cause for peptic ulcer disease (PUD) was unknown in patients. Furthermore, the inhibition of gastric acid secretion was taken as the primary tool for the treatment of PUD.

The classically used experimental ulcer models practically do not accept the histological definition of gastrointestinal ulcers (these models are widely used in the research on ulcer).

The peptic ulcer disease is similar to the infectious disease caused by *Helicobacter pylori* – in terms of classical (and old) terminology of this disease – which can be accepted partially, and now classical eradication treatment seems to be successfully used in the medical treatment (for details, see Mózsik et al., 2014 a, b, c, d). No clear histological evidence has been given by international experts that the infections caused by *Helicobacter pylori* produce histologically "classical" ulcer.

However, there is no doubt that many results of classical human observations were given earlier, and these results remained with us after Garrick and Warren received the Nobel Prize in 2005 [for the etiological role of *Helicobacter pylori* infection as a causative (or main) factor to human peptic ulcer disease]. During that time, the attention of physicians was only focused

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on reality to prove the role of *Helicobacter pylori* infection. This approach suggested two different important points, namely, a). the eradication treatment was widely accepted in every medical practice and b). the results of classical gastroenterological research were forgotten after 2005 (when Warren and Garrick received the Nobel Prize for their research with *Helicobacter pylori*) in our everyday medical practice.

Clinicians have very frequently met patients with gastrointestinal mucosal damage, who obtained different drugs (dominantly non-steroidal anti-inflammatory compounds). The histological features of these drug-induced gastric mucosal damages do not indicate the classical ulcer structures.

The term "peptic ulcer" is not used in everyday medical practice. The characterization of ulcer by the name of "peptic" potentially suggested the overproduction and function of pepsin in the development of ulcer diseases.

11.2. Clinical pharmacology

Our interest in peptic ulcer disease started in the 1960s. We studied different clinical symptoms, functional parameters of the stomach and small intestine, "actual traditional medical treatment", and efficiency of different drugs used in the medical treatment of peptic ulcer (gastric ulcer, duodenal ulcer, typical complaints of detectable symptoms resembling hyperacidity; however, no ulcer was detectable).

In the 1960s, there was no methodology to approach these complicated fields of gastroenterology; however, there was hope that a new tool would be invented.

The basic problems of human clinical pharmacology are the following: measurements of absorption, metabolism, excretion of different drugs, serum levels of drugs and to find correlations between the obtained clinical pharmacological parameters and drug actions (inhibition of gastric acid secretion, gastric emptying, healing rate, side effects). Our studies started with the establishment of methodology for parasympatholytics in the 1960s. These observations enabled in excluding different drugs from the human "classical medical treatment," because these compounds were not absorbed from the gastrointestinal tract.

The classical pharmacological research tried to produce new quaternary ammonium compounds (instead of tertiary ammonium compounds). The theoretical background of these research works was as follows:

1. To produce drugs having long-lasting drug actions (the therapeutic time interval of atropine is 4–5 hours) in the medical therapy;
2. The tertiary ammonium compounds can pass across the hemato-encephalic barrier, while the quaternary ammonium compounds cannot pass over across this barrier;
3. The quaternary ammonium compounds produced have stronger blocking effects on peripheral neural ganglions than those produced by tertiary ammonium compounds.

Clinical pharmacological studies have proved clearly that the absorption of quaternary ammonium compounds from the human gastrointestinal tract is bad (or not absorbed). We

received a clear explanation for why some drugs are without any objective effects in the human medical therapy (so we received another explanation from our observations why different indications resulted in gastric surgery for peptic ulcer). We had a quaternary ammonium compound (Gastropin®) in our medical practice (at that time) which is absolutely not absorbed from human GI tract (e.g., 1000 pills given orally); however, when this drug was given as injection, we were able to detect its serum level and excretion of the drug in the same person.

On the contrary, the results of our previous clinical pharmacological examinations demonstrated clearly that the results of experimental pharmacological research cannot be applied directly to the human medical therapy.

One of the most important results was (obtained by clinical pharmacology) that the duodenal ulcer completely healed during classical atropine treatment in patients with duodenal ulcer; however, the gastric acid secretory responses of these patients were unchanged (1965). It was also important to emphasize that the clinical pharmacological parameters of atropine treatment were also unchanged.

Another important question was in medical therapy (especially after establishing the clinical pharmacological methodology). "What kind of therapy" can be taken as "basic therapeutic state"? In other words, what happens to patients who are not given an effectively acting drug (or compounds)? Halter and coworkers published a paper in gastroenterology (Scheurer et al., 1977), which described that gastric and duodenal ulcers were able to heal without the administration of any drug (however, the description of this placebo compound – without any pharmacological actions – was not clearly defined chemically in the aforementioned paper).

In our clinical pharmacological practice, we used an antacid tablet (without the neutralization capacity of gastric acid secretion) as placebo drug (aluminum hydroxide).

In randomized and prospective studies, the efficiencies of atropine (3 × 1–2 tablets/day orally given), cimetidine (1.0 g/day orally given), carbenoxolone (3 × 100 mg/day orally given for 2 weeks and 3 × 50 mg/day orally given for 3rd and 4th weeks) and placebo (3 × 1 placebo tablet/day orally given) for one month was analyzed. Different laboratory examinations, such as gastrofiberoscopic examinations (the presence of ulcer was detected, and the measurement of ulcer size was carried out planimetrically), were carried out at the beginning, 2nd and 4th weeks of the study, while dairy card observations (complaints, appetite, body weight,, etc.) were recorded day to day from patients with duodenal ulcer during the whole time period of the study (Tárnok et al., 1989).

The results of this study clearly indicated the following:

1. The beneficial effects of atropine, cimetidine and carbenoxolone were superior to that of placebo in a multicenter, randomized, prospective and comparative study in duodenal ulcer (DU) patients;

2. No significant difference was obtained in the beneficial effects of atropine versus cimetidine versus carbenoxolone in DU patients;

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3. Because the carbenoxolone has no inhibitory action of gastric acid secretion in DU patients, the ulcer healing effects (due to stimulation of mucus) could be considered independent of any effect on gastric acid production (Tárnok et al., 1979; Mózsik et al., 2011).

Thus, these and earlier demonstrated studies of chronic atropine treatment in DU patients (during the 1960s–1970s) were performed before the classical concept of "gastric cytoprotection" was formulated by André Robert, yet it is clear now in retrospect that we had been observing acid-independent gastroduodenal protection with atropine and other drugs before Robert et al. had defined gastric cytoprotection (1979).

On the contrary, these observations clearly indicated us that the beneficial effects of different drugs (or drug candidates) were compared to that of placebo effect. This was the first step in the gastrointestinal clinical pharmacology, when the effects of different drugs (compounds) were compared to that of placebo. In our days, the basic requirement for new drug production is that the suggested beneficial effect should be better than that of the most effective drug in different medical fields.

Clinical pharmacology offers a new possibility to suggest a proof for the development of tolerance (Mózsik et al., 1965 a, b, 1966 a, b, c, 1969 a, b, c, d, e, f) and cross-tolerance (Mózsik and Jávor, 1968 a, b, 1969 a, b, c, d, e, f) without any inhibition in gastric basal and supraliminal (but submaximal) stimulated gastric secretory responses in patients with chronic GI ulcers (Mózsik et al., 1966, a, b, c, 1970 a, b, c). In other words, the PUD healed without any inhibition of gastric acid outputs (so clearly the PUD healed just on the dependence of gastric mucosal protective mechanisms).

The facts for the existence of "gastric cytoprotection" were generally and clearly indicated by the works of Robert et al. (1979) in experimental observations in rats. This phenomenon was proved specifically to prostaglandins in rat observations (Grossmann, 1979).

The gastric mucosal healing without any inhibition of gastric acid secretion was proved by our team with anticholinergic cimetidine and retinoids in animal observations (Jávor et al., 1981; Mózsik, 2005; Mózsik et al., 1967c, 1969a; Morón et al., 1984c) and in patients (Rumi et al., 1997, 2001 a, b).

We also demonstrated – in randomized multiclinical, multicentric and prospective study in gastric ulcer patients – that vitamin A (3 × 50.000 IU/day orally given) has an ulcer healing effect in GU patient (without any gastric acid inhibitory action) (Patty et al., 1982, 1983; Mózsik et al., 1986). Vitamin A is an important nutritional component having scavenger properties (Mózsik et al., 2005, 2007).

To the best of our knowledge, this study was first carried out in multiclinical, randomized and prospective study with nutritional components (as scavenger) in patients worldwide.

Clinical pharmacology studies helped us in comparing the beneficial effects of different drugs in gastric and duodenal ulcers in patients. The key roles in these clinical pharmacological studies were the follow-up of changes in the incidence of ulcer sizes at different times of randomized, multiclinical, prospective and multiclinical studies. To understand and evaluate

the dynamism of ulcer healing rates of different drugs, clinical pharmacological studies of the changes of ulcer sizes in incompletely healed patients are necessary.

The general hypothesis (the increased side of aggression, that is, the overproduction of HCl secretion) responsible for the development of GI ulcers in patients was applied for many years. As we can see from the literature and our observations, this standpoint has been invalid both in animal experiments and in patients (Mózsik et al., 1985).

11.3. Biochemical results of the human gastrointestinal tract

After obtaining the new clinical pharmacological results in patients with gastric and duodenal ulcer, it was another important standpoint that the classical gastric and duodenal ulcers develop as a result of tissue hypoxia (like myocardial infarction). However, it was also interesting to note that many drugs (used in the medical treatment of peptic ulcer) inhibit the biochemical metabolism of gastrointestinal mucosa (parasympatholytic drugs, histamine$_2$ receptor blockers, later the proton pump inhibitions). As it is well known, these compounds inhibit the breakdown of energy storage molecule (adenosine triphosphate, ATP). In other words, these drugs inhibit the liberation of energy (by splitting up of ATP into ADP). However, it was (and is) suggested that the resynthesis of ATP can be inhibited under hypoxemic conditions in GI mucosal tissues. Therefore, we medically applied different drugs in the medical treatment of peptic ulcer, which was a priori able to inhibit the metabolic adaptation. Our primary aims were to stimulate positive metabolic adaptation. The aims of medical treatment and suggestions in the development and healing of gastric and duodenal ulcers are absolutely in contradiction. These (and other) arguments and counter-arguments (or suggestions) led us to start with the biochemical examinations of gastrointestinal mucosal tissues.

It is important to learn the basic methodologies applied in the biochemical examinations in GI mucosal tissues. We tried to follow up the updated, so-called general, trends in the biochemical observations. We have to emphasize that the progression of biochemical research (in detail) is practically an impossible challenge for clinicians. In consequence of many circumstances, we started with simple biochemical examinations of gastrointestinal mucosa from 1966. We spent more time in learning these biochemical methodologies in animal experiments (see Chapters 3, 4 and 5).

Our basic standpoints were, during the "learning" period, to learn and demonstrate the involved cellular mechanism of gastrointestinal mucosal damage and prevention. The results of many of our biochemical observations proved that the cell membrane, mitochondrion, proteins, RNA and DNA are involved in the development of gastric mucosal damage and prevention in animal experiments.

Probably the best representative key moments in these tissue reactions were to understand the details of the changes in cellular energy systems under different pathological and experimental conditions. The acid-soluble inorganic and organic phosphates were measured in GI mucosa. The components of acid-soluble organic phosphates were not known in the earlier times (in the 1960s–1970s). Later, we could separate adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP) and adenine–adenosine from the acid-soluble

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organic phosphates. Consequently, we were able to not only follow up with the changes to the extent of ATP transformation into ADP but also approach the possible extent of rephosphorylation. Similar observations were made by Atkinson (1968) to approach the general metabolism of living cells, including some calculation index from the results of measurements [such as ATP/ADP, adenylate pool (ATP+ADP+AMP), "energy charge" (ATP + 0.5 ADP)/(ATP+ADP +AMP)]. The calculated values of "energy charge" give information on the extent of phosphorylation (and dephosphorylation). When the value of "energy charge" is equal to 1, then all adenosine compounds are phosphorylated (e.g., in the form of ATP); however, if its value is 0, then all adenosine compounds are in dephosphorylated form (e.g., practically not in the form of ATP). The results of these observations gave us a possibility to prove (or to exclude) the presence of tissue hypoxemia (which was a key point in the development of mucosal damage during ulceration).

Biochemical observations from the resecates of human gastrointestinal tract after the surgical intervention in patients with peptic ulcer were carried out in the 1970s (see Chapter 7 for details). These biochemical examinations were performed under the nationally accepted medical practice, our scientific knowledge and ethical laws; however, our methodological abilities were limited by the current knowledge in medicine (e.g., no possibility for cAMP).

From the evaluation of these biochemical examinations, we emphasize the following:

1. Simultaneously 6–10 biochemical measurements were performed (from the same resecate obtained from a patient);
2. All biochemical examinations (measurements of ATP, ADP, AMP, lipid phosphates, RNA and DNA preparation of membrane ATPase) – from the tissue of one patient – were simultaneously carried out;
3. Tissue samples obtained by biopsy were not suitable enough for simultaneously carried measurements (the technical problems of the measurements were excluded by these simultaneously carried out biochemical examinations).

All biochemical examinations from the gastric tissues (obtained from one patient) were also simultaneously carried out.

There are different important points applicable from the biochemical methodology from 1969–1970, when we learned the existence of the details of the specific sodium pump (substrate enzyme with its classic biochemical behaviors) and "second messenger" systems in other tissues (as GI tract). Because we succeeded in preparing the classical Na^+–K^+-dependent ATPase and adenylate cyclase from rat heart muscle, rat and human gastric mucosa, we received an absolutely new possibility to understand some parts of regulations of cellular energy systems (Mózsik and Øye, 1969; Mózsik, 1969 a, b, 1970; Mózsik et al., 1970 a, b).

We were the first authors to prove the presence of Na^+–K^+-dependent ATPase (Mózsik and Øye, 1969; Mózsik, 1969 a, b) and adenylate cyclase (Mózsik et al., 1970) in rat and human gastric fundic mucosa (Gheorghui, 1976; Mózsik et al., 1975 a, b, 1976 a, b, 1978 a, 1982 a, b).

These observations were carried out in earlier time period under different *in vitro* conditions to describe the existence of feedback system between two membrane-bound ATP-dependent

energy systems (Mozsik, 1969 a, b, 1970 a, b). We also measured the changes in these energy supply systems by the direct *in vivo* measurements of different adenosine compounds by different enzymatic kits and RIA method (such as ATP, ADP, cAMP, AMP) in the gastrointestinal tract. (We did not have these conditions at the time of our human biochemical examinations.)

Because no systematic biochemical examinations from the human gastrointestinal tract were carried out and published, out attention is focused on the results obtained from GI resecates of human GI tract obtained at the time of surgical intervention (treatment) in peptic ulcer patients.

There are important notes to the evaluation of human biochemical results obtained from the GI resecates of patients with peptic ulcer:

1. We had no information (at the time of gastric resection) on the suggested etiological factors for this disease;

2. The gastric secretory responses (basal acid output, BAO; maximal acid output, MAO) were – as the gastric secretory responses and the suggested main aggressive factor for peptic ulcer disease – permanently measured in these patients. The extents of these secretory responses were used to create different groups of biochemically evaluated patients;

3. We had no information on the presence of *Helicobacter pylori* infection in these patients. Now we know well that practically all DU patients were infected with *Helicobacter pylori*, and its infection rate is less in GU patients. In our days, we had no knowledge on *Helicobacter pylori* infection in jejunal ulcer patients (after Billroth II-type surgical intervention);

4. We had no information on the details of medical treatment (applied drugs, time periods of medical treatments) on GI mucosal cells in the ulcerated and control animal and patients' tissues;

5. The necessary indication for surgical intervention was done based on a special consultation between the internist and the surgeons; however, we did not participate personally in this process;

6. In the critical evaluation of ATP, membrane ATPase, and ADP, the possible role(s) was used as an energy supply system (namely energy liberation) for different regulations of enzymes and a critical biochemical parameter of GI tissues to prove (or to exclude) the presence of tissue hypoxemia (by the measurements of dephosphorylation and oxidative phosphorylation). This enzyme system exists in all animals tissues;

7. We wanted to know more on the biochemical structure of cells in the human GI tract in peptic ulcer patients.

8. An important fact is that the Na^+–K^+-dependent ATPase and H^+–K^+–ATPase differ from each other; however, the ATP is a common substrate for the function of both enzymes (see Chapter 5);

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9. The activity of membrane ATPase (ATP transformation into ADP by Na^+–K^+–ATPase) and its extent can be used as an important energy biochemical marker function related to the functional state and to the general buildup of target organs;

10. The H^+–K^+–ATPase is located only in the parietal cells of the stomach (see Chapter 5) and not in other cells of the GI mucosal tissue.

The results of human biochemical examinations (from the resecates of GI tract) indicated clearly that:

1. A very close and positive correlation exists between the Na^+–K^+-dependent ATPase activity (liberated quantities of inorganic phosphate from ATP by Na^+–K^+-dependent ATPase, measured in *in vitro* conditions) versus gastric basal acid output (BAO)(r = 0.88; regression line: $Y = 0.49 + 0.39.X$; n = 45) (Mózsik et al., 1974d).;

2. The Na^+–K^+–ATPase system (from the human gastric fundic mucosa) works without any trouble under cholinergic influences (Mózsik et al., 1974c) and its activity can be inhibited by parasympatholytics, histamine, pentagastrin, PGE_1 and PGE_2 (Mózsik et al., 1974b; Mózsik et al., 1974a), epinephrine (Mózsik, 1969 a, b).;

3. There are positive and significant correlations between the BAO, MAO values and members of ATPase systems (Na^+–K^+-dependent ATPase activity, tissue levels of ATP and ADP in the human gastric fundic mucosa – including the positive correlations between these biochemical parameters) (Mózsik et al. 1981).;

4. The ATP transformation into ADP by Na^+–K^+–ATPase system can be regulated by drugs, hormones and mediators in smaller molar concentrations than the ATP transformation into cAMP by adenylate cyclase, and the drug actions are contraregulatory in these energy systems (Mozsik et al. 1997c).

5. The gastric acid secretion depends on the activation of Na^+–K^+-dependent ATPase and stimulation of adenylate cyclase, besides the activation of function of H^+–K^+–ATPase in human beings.

6. The active transport functions across the gastric mucosal cells depend on different cellular (however, ATP-dependent membrane-bound) energy systems (such as Na^+–K^+-dependent ATPase-, adenylate cyclase- and H^+–K^+-dependent ATPase systems) in human beings.

7. Biochemical and energetic gradients exist in the gastric fundic, antral, duodenal (jejunal) mucosal tissues dependent on the gastric basal acid secretory responses in patients with hyperacidity and normacidity; however, these gradients disappear in patients with hypoacidity (Mózsik— et al., 1976).;

8. The extents of ATP transformation into ADP by membrane ATPase are significantly higher in the mucosal tissues around the gastric (antral), duodenal and jejunal ulcer patients than those in their identical normal (non-ulcerated) mucosal tissues (in the same patients) (the values of "energy charge" remained unchanged in these tissue specimens). These results together proved clearly that the oxidative phosphorylation is intact in the ulcerated mucosa, which cannot be obtained in the presence of hypoxemic damage in the tissues.

For understanding these results, we have to mention different points:

1. We had no information on the existence of classical ulceration in the antrum, duodenum and jejunum in patients;

2. We had no information on the kinds (and their time periods) of medical treatments;

3. We did not receive any information on the reasons for the indication of surgical intervention in these patients;

4. We also had no suggestion on the possible healing processes of ulceration in these patients without any surgical intervention;

5. During surgical interventions, we did not hear anything on the presence of *Helicobacter pylori* infection; however, now it is clear that the incidence of *Helicobacter pylori* infection differs in the case of duodenal ulcer and gastric ulcer (no data are available on *Helicobacter pylori* infection in jejunal ulcer after surgical intervention in patients). Based on our opinion on these, we suggested that the presence of *Helicobacter pylori* infection is independent of these biochemical observations;

9. Our human biochemical results (obtained in the ulcerated and non-ulcerated mucosa) suggest the positive metabolic adaptation against ulcer development in the antral, duodenal and jejunal mucosa. The extent (capacity) of the metabolic adaptation depends on the general biochemical buildup of the tissues. There is no doubt that the highest metabolic activity can be obtained in the gastric fundic mucosa in patients with gastric hyperacidity and normacidity (because of the existence of biochemical and energetic gradients in these mucosal tissues). Consequently, the exhaustion of antral, duodenal and jejunal mucosa will appear in a shorter time than that in corpus mucosa. Probably that suggestion gives a real explanation for why we applied drugs (having metabolic blocking effect) for the medical treatment of peptic ulcer disease in patients.

We established a uniform biochemical explanation for the development and location of "genuine" gastric, duodenal and jejunal ulcers in patients (Mózsik, et al., 1997b).

9. These results, demonstrated earlier (Figures 67–71), clearly indicated that the extent of ATP–ADP breakdown is significantly higher in the ulcerated antral, duodenal and jejunal mucosa specimens than in the control (non-ulcerated) mucosa specimens. This fact can be proven by the increased membrane ATPase activity and increased level of ADP in association with significant increase in the tissue level of ATP. The following facts are found in the background:

   a. No impaired oxidative phosphorylation can be found in ulcerated mucosa specimens, which can be proven by increased tissue levels of ATP in time when the ATP–ADP breakdown was significantly increased (significantly higher membrane ATPase activity and increased level of ADP);

   b. The tissue levels of ATP and ADP are significantly higher in the ulcerated mucosa than those in the non-ulcerated mucosa (in the same patients);

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c. The membrane ATPase activity is also significantly higher in the ulcerated mucosa than that in the non-ulcerated GI mucosa (Mózsik et al., 1979);

d. The higher ATP tissue levels (in time when the ATP breakdown was increased in both directions) can only be obtained by the intact oxidative phosphorylation pathway;

e. The biochemical components of gastric mucosal tissue were expressed in accordance to 1.0 mg DNA, which represents the same number of cells (Figure 157). The values of adenine–adenosine, ATP, ADP and AMP were increased in the gastric fundic mucosa in patients with increased gastric secretory responses (BAO, MAO) and in the mucosa around chronic antral, duodenal and jejunal ulcer (Mózsik et al., 1979 a, b, d, f, h, 1981 a, b, 1987 a, b; Nagy et al., 1978, 1981b);

f. No physiological data exist in the literature to prove the presence of decreased GMBF in the gastric fundic mucosa in patients with gastric hyperacidity; nobody found an increased tissue level of lactate. Experts accept the increased energy turnover (increased capacities of ATP–ADP and ATP–cAMP transformation) in these gastric fundic mucosa specimens.

The chemical comparison of the biochemical results obtained in the human gastric fundic mucosa with different gastric acid secretory responses and non-ulcerated and ulcerated antral, duodenal and jejunal mucosa in patients is shown in Figure 297. The results are expressed as amounts of biochemical parameters/1 mg DNA.

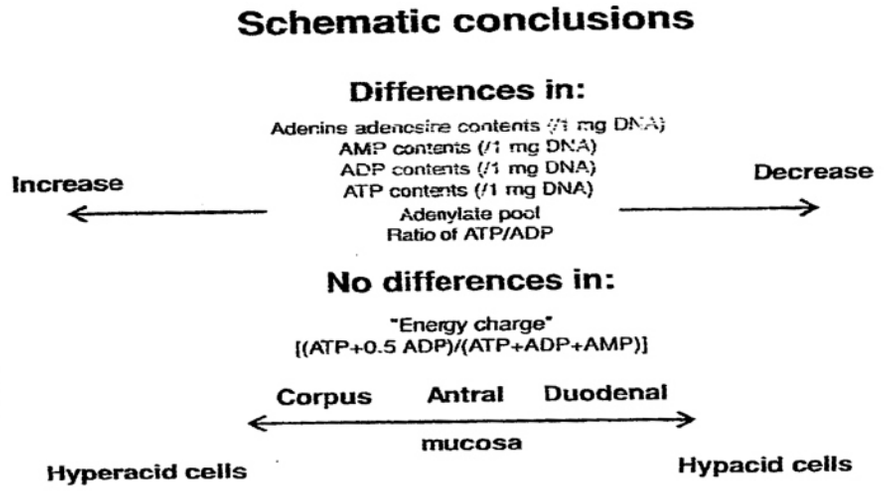

Figure 297. The schematic presentation of biochemical buildup of human gastrointestinal mucosa in patients with different gastric acid secretory responses. All of the adenine and adenosine compounds increased significantly (meanwhile the stream of ATP breakdown enhanced in both directions) in the gastric corpus mucosa in comparison with those results obtained in corpus mucosa patients with hyperacidity. The same biochemical parameters were obtained in the ulcerated antral, duodenal and jejunal mucosa in patients with chronic antral, duodenal and jejunal mucosa. So the biochemical structure of human chronic antral, duodenal and jejunal mucosa is the same as that obtained in the corpus fundic mucosa in patients with gastric hyperacidity. [Mózsik, Abdel-Salam, Király, Morón, Nagy, Sütő, Tárnok, Jávor (1997) in Mózsik Gy., Nagy L., Király Á. (eds) Twenty Five Years of Peptic Ulcer Research in Hungary: From Basic Sciences to Clinical Practice (1971–1995) pp. 159–170., Akadémiai Kiadó, Budapest; Mózsik, 2006. In: Discoveries in Gastroenterology (1960–2005). Akadémiai Kiadó. Pp. 139–224 (with kind permission).]

The biochemical buildup (chemical composition) of cells in the human gastric fundic mucosa with hyperacidity and in the ulcerated antral, duodenal and jejunal mucosa in patients are significantly different from that in gastric fundic mucosa with hypoacidity and in non-ulcerated antral, duodenal and jejunal mucosa. In consequence of these facts, the physiological, neural, hormonal and pharmacological regulations of these cells in the human gastric fundic mucosa in patients with hyperacidity and in ulcerated antral, duodenal and jejunal mucosa also differ (quantitatively) as those in the cells in gastric fundic mucosa with hypoacidity and in non-ulcerated antral, duodenal and jejunal mucosa in peptic ulcer. The physiological, pharmacological and pathological regulations of membrane-bound ATP-dependent energy systems had essential roles in these processes.

How can we explain the contradictions of the presence and absence of ulcerated gastrointestinal mucosa in animals and patients with peptic ulcer?

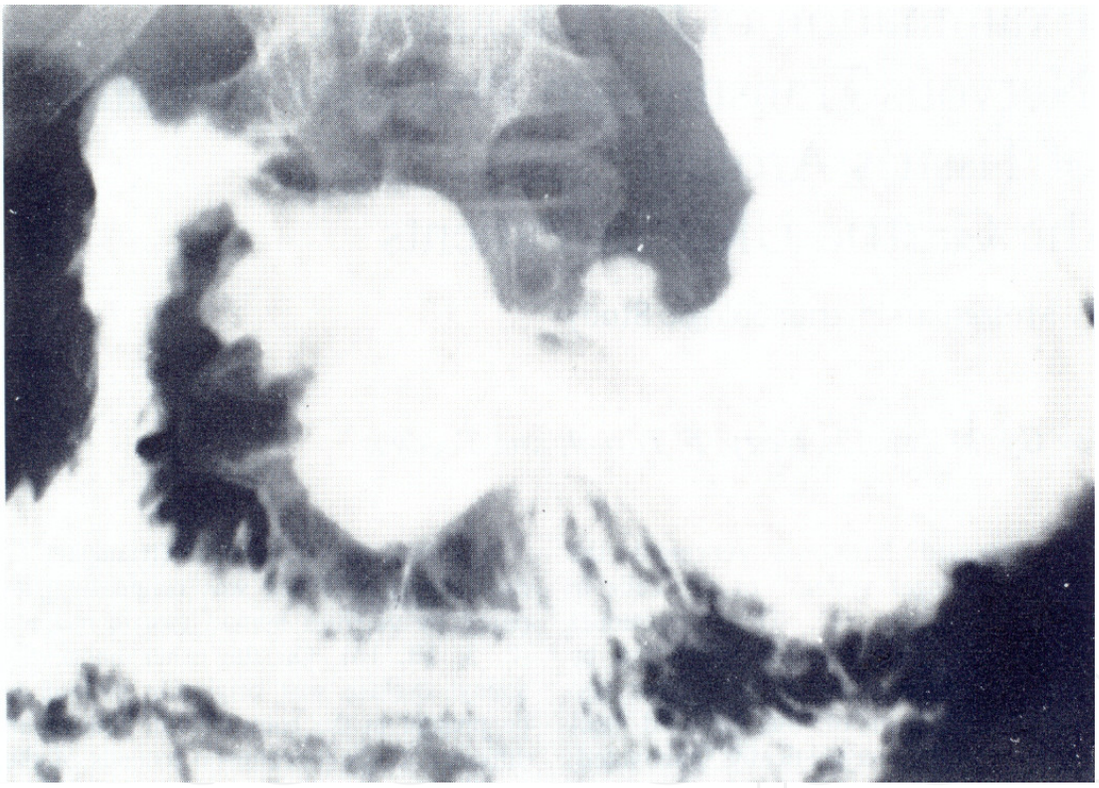

Figure 298. Roentgenogram of gastric ulcer localized on the lesser curvature of the stomach of a 56-year-old patient. The X-ray examination was performed by Z.Molnár M.D. at the Radiological Department, University of Medical School, Pécs, Hungary, in 1970. [Mozsik, Nagy, Tárnok , Jávor (1971): In: Pfeiffer C.J. (Ed). Peptic Ulcer. Munksgaard, Copenhagen – Lippincott, Philadelphia. pp. 323–328 (with kind permission).]

1. The results of experimental measurements in the animal gastrointestinal mucosa (used different – dominantly physiological – different experimental conditions, but not under the development of mucosal damage) and there bewer were proved the causative correlation between the physiologically measured decrease of GMBF versus insufficiency of oxidative phosphorylation in the same tissue samples in the same time (Kitajima, 1989);

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2. The experimental evidence of decrease in tissue ATP has been based on the observations of Menguy et al. (1974 a, b, c, d); however, the examined animals had a severe blood loss in the experiments. No similar changes of blood circulation existed in other experimental models (used by different experts all over the world);

3. The measurement of the tissue level of gastrointestinal mucosal tissues alone cannot give a scientific evidence for the existence of impaired oxidative phosphorylation (see Mózsik and Vizi, 1976 a, b; Mózsik et al., 1983). We have to measure the tissue levels of ATP, ADP, AMP and cAMP together (with the simultaneous measurement of lactate) in the same tissue samples in the same time;

4. The biochemical structures of the human gastric fundic mucosa with increased gastric acid basal (BAO) and maximal (MAO) secretory responses are the same as those obtained in the ulcerated antral, duodenal and jejunal mucosa in patients with peptic ulcer;

5. The tissue levels of ATP in the antral, duodenal and jejunal ulcerated mucosa are much higher than those in the non-ulcerated (control) mucosa. On the contrary, the tissue levels of ADP – in these tissue samples – are the same as ATP. However, the membrane (transport) ATPase (Mg^{2+}-dependent, Mg^{2+}–Na^{+}–K^{+}-dependent and Na^{+}–K^{+}-dependent) activities are also significantly higher in the ulcerated mucosal tissues than those in the control (non-ulcerated) ones.

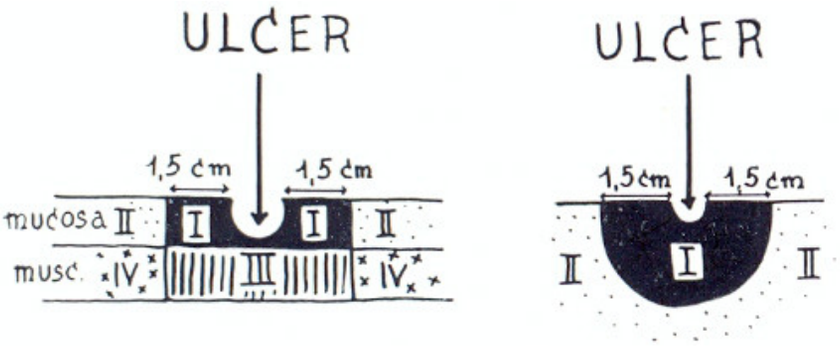

Figure 299. Schematic presentation of separation of gastric tissue surrounding a gastric ulcer localized on the lesser curvature of the stomach (same patients as in Figure 298). The left-hand side figure shows the transaction of the gastric wall; the right-hand side figure indicates the surface of the gastric mucosa. The gastric mucosa was separated from the muscular layer, and both layers were separated into two parts: gastric mucosa up to 1.5 cm around the gastric ulcer (I); gastric mucosa without ulcer (II); "callus" (III) i.e., the muscular layer under the gastric ulcer; and muscular layer (IV), i.e., the muscular layer under the gastric tissue without ulcer. These specimens of gastric tissues were used for the preparation of Na^{+}–K^{+}-dependent ATPase. [Mózsik, Nagy, Tárnok, Jávor (1971): In: Pfeiffer C.J. (Ed). Peptic Ulcer. Munksgaard, Copenhagen – Lippincott, Philadelphia. pp. 323–328 (with kind permission).]

The following main biochemical events are incorporated by these observations:

a. The increased membrane (transport) ATPase in the ulcerated antral, duodenal and jejunal mucosa produces an increased tissue level of ADP in these tissue samples;

b. The increased tissue levels of ATP in the ulcerated antral, duodenal and jejunal mucosa were compared with those in the non-ulcerated (control) mucosa tissue specimens;

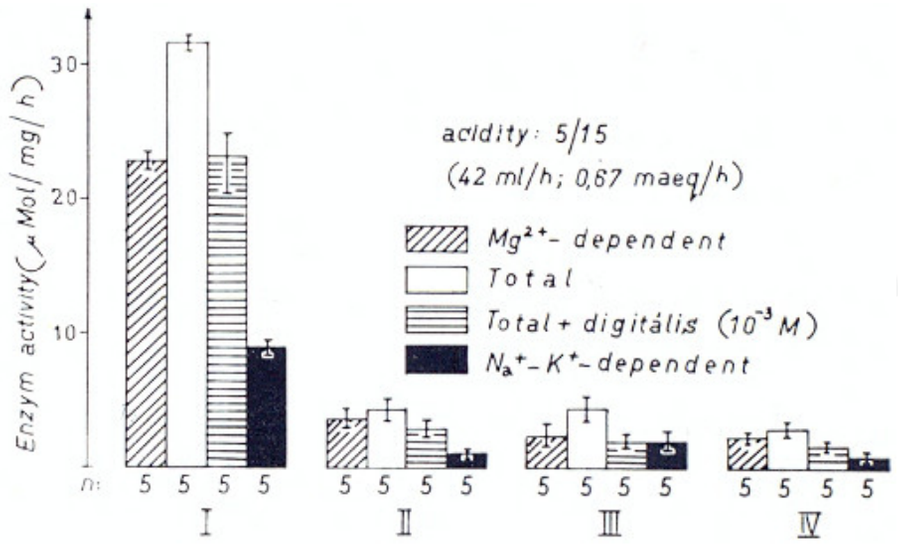

Figure 300. Alterations of the Na^+–K^+-dependent ATPase (transport) ATPase in the gastric tissues around the gastric ulcer in a patient. The ATPase activity was measured by the liberation of inorganic phosphorus and expressed in μMol/mg "dried membrane material"/hour. Secretory characteristics of the patient: volume of gastric secretion: 42 mL/hour; acidity, 0.67 mEq/hour or 5/15 clinical units, unstimulated; n, number of examinations (results presented as means ± SEM of five experiments). [Mozsik, Nagy, Tárnok, Jávor (1971): In: Pfeiffer C.J. (Ed). Peptic Ulcer. Munksgaard, Copenhagen – Lippincott, Philadelphia. pp. 323–328 (with kind permission).]

c. The existence of increased tissue levels of ATP with ADP and increased membrane (transport) ATPase activity gave a clear evidence for the increased (not impaired) oxidative phosphorylation in the ulcerated antral, duodenal and jejunal mucosa tissue specimens (excluding the presence of tissue hypoxia in the mucosal tissues around the antral, duodenal and jejunal ulcers in patients).

6. The GMBF increases with the increase in gastric acid secretory responses in human beings (Jávor, 1968).

The first molecular-pharmacological–biochemical examinations in gastric ulcer of patients with gastric ulcer was internationally demonstrated by us in 1970 at the 4th World Congress of Gastroenterology which was located in Copenhagen, Denmark (Mózsik et al.., 1971b). The forthcoming figures show these memory presentations (Figures 298–301). (Note: we did not mention – at that time – that the transformation of ATP into cAMP is probably also present in cases of higher molecular doses of atropine for the real explanation in the form of atropine-induced-inhibitory action curve on the Na^+–K^+–ATPase activity.)

11.4. Results of biochemical-pharmacological studies in animal experiments

The animal observations were carried out simultaneously with human observations. The rats were used for these observations (under the national law regulatory conditions). A majority of animal experiments were used as acute models, while the characteristics of peptic ulcer were used for chronic experimental models (in dogs dominantly) (see Table 45).

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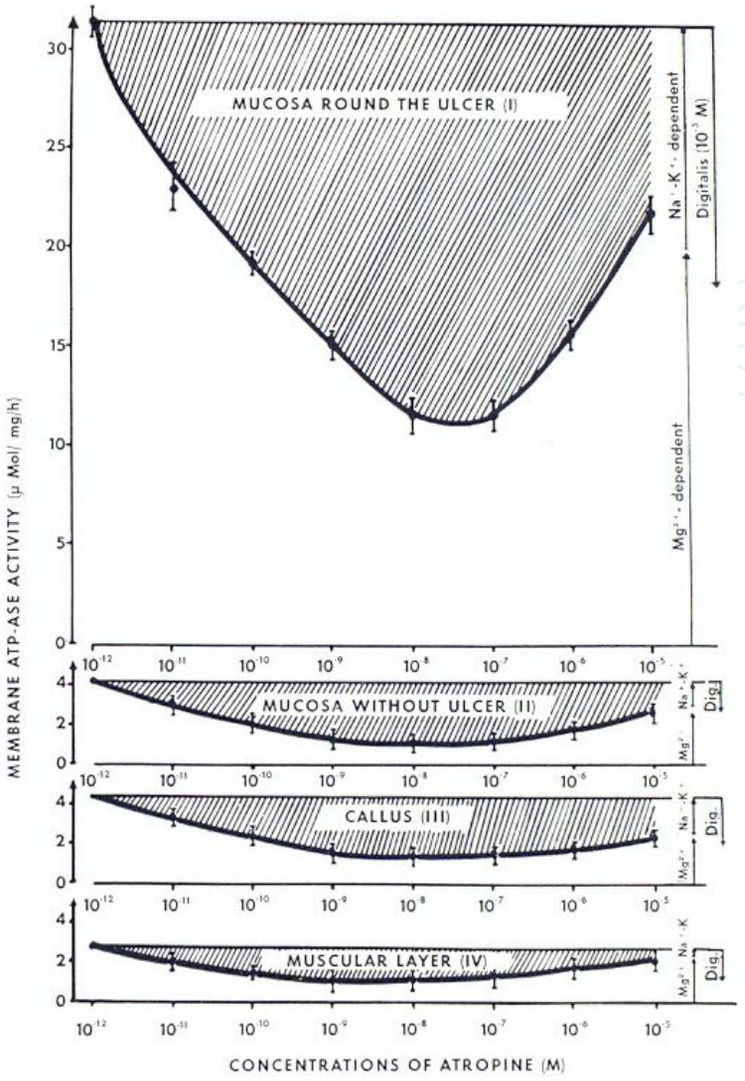

Figure 301. Inhibitory effect of atropine on Na^+–K^+-dependent ATPase activity prepared from different regions of gastric tissue around the gastric ulcer in the patient. The ordinate shows the ATPase activity by liberated, inorganic P, in μMol /mg dried "membrane material"/hour, atropine. Each point on the curves represents the means ± SEM of 5 experiments. The arrows on the right-hand side of the figure indicate the increased membrane ATPase by Na^+ (80 mM) and K^+ (33 mM) and the decreased activity of membrane ATPase by ouabain (10^{-3} M). [Mózsik, Nagy, Tárnok, Jávor (1971): In: Pfeiffer C.J. (Ed). Peptic Ulcer. Munksgaard, Copenhagen – Lippincott, Philadelphia. pp. 323–328] (with kind permission).]

To elucidate the pathomechanism of human peptic ulcer, and to find effective drugs to treat patients, a series of animal models have been devised to mimic the natural history of ulcer disease. Unfortunately, the results contained – if not all – in these techniques do not process the main characteristics of human ulcer disease.

In spite of important differences, we do not have better direct methods for tackling the problems of ulcerogenesis than to use animal models. Generally, we use the expression of "experimental ulcer" for all sorts of experimentally induced gastric mucosal lesion irrespective of the true nature of the damage (erosion, acute and chronic ulcer). However, it is highly

Main characteristics of Peptic ulcer disease	Experimental chronic gastric ulcers
- Appears unexpectedly	- No spontaneous gastric ulcer in animals
- May heal spontaneously	- Rapid healing after withdrawal of The ulcerogenic agent
- Reappear unexpectedly	- Do not reappear
- Gastric ulcre are solitary	- Mostly multiple
-Antral localization (mainly)	- Mainly in the fundus
- Role of Helicobacter pylori duodenal ulcers	- No proofs of Helicobacter pylori influence

Table 45. Natural history of human ulcer disease and the experimental techniques, which do not process the main characteristics of the human disease.

important to differentiate between these three types of gastric lesions in both animal and man as their pathomechanisms are different. Erosions and acute ulcers differ from the chronic ones due to the underlying cause, which is mostly known. If properly treated, they disappear rapidly and do never become chronic. This does not mean that they represent harmless conditions; sometimes it might be difficult to treat them, and they may cause massive bleeding, perforation or even death.

The rat stomach is, however, quite different from that of the man, and the same is true for guinea pigs and other small rodents. The animals best suited for ulcer research are monkey, pigs and dogs. Even in these animals, there are some peculiarities that hamper the evaluation of the results, but with some precautions, the data obtained with some methods might be extrapolated to man. We had possibilities to do experimental observations only in rats, and consequently we were able to carry out acute observations. Biochemical pharmacological observations were carried out in rats under different experimental conditions.

Our attention was focused on evaluating the following:

1. The changes in the biochemical parameters of gastric tissues before the development of gastric mucosal lesions (produced by surgical intervention or administration of different drugs and chemicals) without and with administration of any protective drugs;

2. The study of interrelationships of the Na^+–K^+-dependent (transport) ATPase system (ATP transformation into ADP by membrane ATPase) and "second messenger system" (ATP transformation into cyclic 3′,5′-adenosine monophosphate by adenylate cyclase) in gastric tissues during the development of mucosal damage and its protection;

3. The study of the role of vagus nerve of "surgical" and "chemical vagotomy" in mucosal protection against different drugs and chemicals;

4. The time-sequence study for the evaluation of oxygen free radicals and scavengers in the gastric tissues in acid-dependent and non-acid-dependent gastric ulcer models;

5. The presence (or absence) of tissue hypoxia in gastric tissues under different experimental conditions;

6. The comparative study for the actions of different drugs with different well-known subcellular mechanisms in gastric acid secretion, in the ethanol-induced model and prostacyclin-induced gastric mucosal protection in the ethanol-induced model.

The methodological problems (designs) and biochemical assays were detailed in some chapters.

We indentified very simple questions to clear these different scientific problems in the chapters, and we tried to give correct(s) answers to our previous questions in acute experiments. We are sure that we cannot give correct answers to the questions asked after chronic biological and pathological processes. We had to learn these methodological and scientific problems from human clinical pharmacology and human biochemical examinations of the resecated tissues of gastrointestinal tract (in patients who underwent the gastric surgery because of peptic ulcer disease). We tried to collect some important information from the ulcer research (including the results in animal experiments and human observations) in animal experiments.

Main discussion points of animal experiments are as follows:

1. The significant changes of membrane-bound ATP-dependent energy systems appear earlier in time in the rat gastric mucosa than those in the development of peak value of gastric acid hypersecretion of an ulcer development in 24-hour pylorus-ligated rats. The extent of ATP transformation into ADP by membrane ATPase increased, in association with decreased ATP transformation into cyclic AMP by adenylate cyclase in the gastric (fundic mucosa and forestomach) tissues in above-mentioned times of experiments (for further information, see Section 8.1.1).

When ouabain (as a specific drug to inhibit the Na^+–K^+–ATPase) was used in this experimental model, we found significant inhibition on both gastric acid secretion and ulcer development. Furthermore, these actions of ouabain also appeared in the same time as those in the untreated animals.

The results of these observations clearly proved the following:

a. The Na^+–K^+-dependent ATPase system (e.g., ATP transformation into ADP by membrane ATPase) plays a key role in the development of gastric acid hypersecretion and ulcer and in the inhibition (prevention) of gastric mucosal hypersecretion and ulcer production in 24-hour pylorus-ligated rats;

b. The gastric acid hypersecretion response by gastric fundic mucosa appears before the ulcer development of forestomach (rumen), and the inhibition of gastric acid secretion is

also associated with ulcer development in the forestomach (rumen) in 24-hour pylorus-ligated rats;

c. The biochemical changes in the gastric fundic mucosa and rumen – during the development of gastric hypersecretion together with ulcer development and prevention of gastric hyperacidity and ulcer development – indicated similar directions (different in their quantitative values) in both parts of the rat stomach.

2. The surgical vagotomy-induced decrease of gastric acid hypersecretion and the prevention of ulcer development are associated with decreased ATP transformation into ADP by Na^+–K^+-dependent ATPase in 24-hour pylorus-ligated rats.

These results suggest the following:

a. The breakdown of gastric mucosal ATP (both in directions of ATP transformation into ADP by membrane ATPase and of ATP transformation into cAMP by adenylate cyclase) is a basic biochemical background to the development of gastric acid hypersecretion and gastric ulceration and to their inhibitions by surgical vagotomy (for further information, see Section 8.1.2);

b. The measurement of tissue level of ATP (without measurements of tissue ADP, cAMP, AMP) does not give correct information on the approach of the actual levels of cellular energy systems (extents of dephosphorylation and oxidative phosphorylation, presence of tissue hypoxia);

c. The development of ulcer in the forestomach is only a hyperacid secretion process, independently from that of the ulcer location (in this experimental model), and is not related to human pathology of peptic ulcer disease in humans.

The gastric ulcer is located in the antrum of patients with peptic ulcer (which also has no acid secretory ability).

d. The results of the biochemical results (especially to energy supply systems of rat gastric fundic mucosa and forestomach) of 24-hour pylorus-ligated rats indicate a similarity to the biochemical background of the development of human antral ulcer, namely, the biochemical constituents (in terms of energy supply system, which significantly differs in the human gastric fundic mucosa vs. antrum in patients with gastric hyperacidity and normacidity). No antral ulcer can be found in the literature and in our practice (from 1960 to 2014) for the existence of antral location in patients with gastric hypoacidity. The results of biochemical examinations in rats and human gastric (fundic and antral mucosa tissues) give a very closed and acceptable biochemical explanation for antral ulcer development in patients as well as the forestomach of pylorus-ligated rats. These results explain that the gastric ulceration appears as a consequence of gastric hypersecretion (and not after *Helicobacter pylori* infection), which clinically appears after a significantly increased metabolic (energetic) adaptation in gastric tissues (antrum in humans and forestomach in rat). The level of metabolic adaptation in the energy supply systems is limited by the different biochemical structures (and their energetic background) of different parts of the stomach (in both humans and rats). Probably a similar (or the same) explanation is true

for the biochemical explanation of the location of duodenal ulcer in patients (dominantly with hyperacidity) (see results presented in Sections 7.9.2 and 7.10) and jejunal ulcer after Billroth II gastric resection in patients.

3. Molecular pharmacological background of different drug actions in the gastric mucosa of intact gastric tissues under different pathological conditions.

The applications and uses of different drugs were widely used in the physiological, biochemical as well as in the pharmacological research. These methods have been applied to evaluate the characteristics of the effects of new compounds, or physiological events, by the modification in their effects. The atropine application is used to indicate the cholinergic influence and its participation in different physiological phenomena and development of new drugs.

The key points of these studies with "standard drugs" were to measure their actions at the level of final physiological (pathological) effects; however, we have no knowledge on the background of these drug actions. We studied the biochemical background of these "basic drugs" as well as the commonly used experimental standard pathological events (such as pylorus-ligated rats without the administration of any drugs or ethanol-induced gastric mucosa in rats). Our attention was focused on the changes in the membrane-bound ATP-dependent energy systems of the cells.

It was interesting to note that the *in vivo* observations of the interrelationships (extents) between the ATP transformation into ADP and the ATP transformation into cyclic AMP were changed from time to time (in hours in pylorus-ligated rats, in minutes in ethanol-induced model), and there were also absolutely contradictory changes (increased and decreased) between them. The results of these *in vivo* measurements were the same as those obtained by *in vitro* measurements due to the interrelationship of the cellular energy systems.

We had no knowledge on the cellular effects (on membrane-bound ATP-dependent energy systems) of atropine and epinephrine in the gastric mucosa. It was interesting to note that the biochemical background of atropine and epinephrine is very similar to each other; however, their molecular weights differ from each other.

The results of these biochemical pharmacological examinations offered a further explanation for the understanding of significantly different actions of the same drug after its administration during the actual functional (biochemical) state of the target organ (see Sections 8.12. and 8.13.).

4. The biochemical background of aspirin-induced gastric mucosal damage was studied in 4-hour pylorus-ligated rats. Aspirin (200 mg) was dissolved in 2 mL of 150 mmol HCl and intragastrically administered immediately after pylorus ligation. The ATP transformation into ADP significantly increased after pylorus ligation (without the administration of aspirin), while the extent of ATP-cAMP transformation decreased under this experimental condition. After aspirin administration, no metabolic adaptation both in ATP-ADP and in ATP-cAMP system, which can be explained by the direct damaging effect of non-ionized acetylsalicylic acid (as consequence of the presence of weak acid in presence of strong – gastric acid - , and it can to precipitate the membrane of cells), and by partly no

presence of any drug, which would be able to modify the membrane enzyme functions (Figure 90).

The administration of atropine (in doses of 0.1, 0.5 and 1.0 mg/kg) can stimulate ATP transformation into cAMP, which further inhibits the Na^+–K^+-dependent ATPase (besides the direct inhibitory effect of atropine on the Na^+–K^+-dependent ATPase). This active metabolic adaptation of the gastric mucosal tissue (increase in tissue level of cAMP) can produce a protective effect against aspirin (Figures 91–98). It is interesting to note that this metabolic adaptation is only dependent on the ATP–cAMP transformation (without the active participation of ATP–ADP transformation).

Vitamin A and β-carotene are important nutritional components in animals and humans; however, they have no antisecretory properties on the gastric acid secretion (Jávor et al., 1983; Mózsik et al., 1986). These compounds are also present in the aspirin-induced gastric mucosa damage (without any gastric acid inhibitory effects) (Figures 99–110 and Table 40). The biochemical background of these compounds is also similar to that of atropine, namely the ATP–cAMP transformation increased significantly by the application of vitamin A and β-carotene, which produce direct inhibitory action of Na^+–K^+-dependent ATPase (by the increased level of cAMP and AMP). Probably the actual level of ATP can reach to a critical level in the tissues, which can determine the ATP splitting processes by membrane-bound ATP-dependent enzymes.

The contradictory evaluation pathways of these results (obtained with aspirin administration in 4-hour pylorus-ligated rats alone and in combination with atropine, vitamin A and β-carotene) are given in the following:

a. The aspirin-induced gastric mucosal damage is a consequence of any positive metabolic adaptation in the cellular energy systems. The primary explanation given by Davenport (1965), namely the primary role of increased gastric H^+ back diffusion in the aspirin-induced mucosal damage, can be modified by the consequence of the absence of any active metabolic adaptation in the cellular energy systems (which is produced by non-ionized weak acetylsalicylic acid on the cell membranes);

b. If we can produce some active metabolic adaptation by membrane-bound ATPase-dependent energy systems, we can prevent the damaging effect of aspirin (independently on the presence or absence of gastric acid secretion).

5. The observation with indomethacin in different combinations offered further interesting results in the field of experimental ulcer research.

The indomethacin (20 mg/kg s.c. given) causes gastric mucosal damage in fundic mucosa in 4 hours time period. During this time period, the extent of ATP transformation into ADP increased significantly (together with the decreased extent of ATP transformation into cAMP) in the gastric fundic mucosa of rats (without the application of any protective agents).

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The atropine and cimetidine doses together decreased the ulcer development caused by indomethacin in 4 hours time period; however, the biochemical background of the preventive effects of atropine and cimetidine significantly differs in the rat gastric fundic mucosa.

Vitamin A also increases the IND-induced gastric mucosal damage, which is associated with the increased ATP–cAMP transformation. Similar types of observations were made with β-carotene in IND-induced model. With the biochemical background of these observations, we analyzed in detail the correlations between the changes in tissue levels of PGE_2 (its tissue level is inhibited by the application of indomethacin), cAMP, development of IND-induced mucosal damage and prevention of β-carotene. We have observed the following:

a. There was no direct correlation between the tissue levels of PGE_2 versus IND-induced mucosal damage and its prevention by β-carotene;

b. There was a very close correlation between the decreased tissue level of cAMP versus gastric mucosal damage produced by indomethacin (at 1 and 4 hours after indomethacin administration);

c. There was no significant difference between the decreased tissue levels of cAMP at 1 and 4 hours;

d. The indomethacin-induced decrease of tissue level of PGE_2 indicated a tendency to return to the normal level (in untreated animals) during the 4-hour experimental period;

e. The β-carotene-induced gastric mucosal protective effects are dose dependent and closely associated with the increase in tissue levels of cAMP (but not with changes in tissue levels of PGE_2);

f. The gastric mucosal protective effect of β-carotene differs from the prostaglandin system; however, it depends on the positive metabolic biochemical membrane-bound ATP-dependent energy systems.

6. The increased ATP transformation into cAMP (in association with the decreased ATP transformation into ADP) was observed during the development of stress-induced and reserpine-induced gastric mucosal damage in rats. It is also important to note that these changes in the membrane-bound ATP-dependent energy systems are detectable before the macroscopic appearance of gastric mucosal damage;

7. The observations with chemical (96% EtOH, 0.2 M NaOH, 0.6 M HCl and 25% NaCl solution)-induced models allowed us to conclude the following:

   a. The gastric mucosal damage by different chemicals in rats produced the same macroscopic features in the fundic part of the rat stomach, which appears at the same time after the application of necrotizing agents;

   b. There was no difference between the gastric mucosal features (and their characteristics in time and macroscopic pictures) produced by acid-dependent (HCl model) and non-acid-dependent (EtOH model) gastric ulcer models in rats;

c. The ED_{50} doses of PGI_2 (5 μg/kg) and β-carotene (1 mg/kg) (which produce 50% prevention of gastric mucosal damage produced by intragastric administration of 0.6 M HCl and 96% ethanol) were identified in animal experiments. These doses and higher doses were used for studies to evaluate the correlations between the gastric mucosal damage, gastric mucosal biochemistry (ATP, ADP, AMP, cAMP, adenylate pool, "energy charge," ATP/ADP, lactate) and oxygen free radicals (catalase activity, glutathione peroxidase, superoxide dismutase, reduced glutathione and malondialdehyde) in the rat gastric fundic mucosa (see Figures 251–255). These observations were carried out at the same time and the same tissue samples were used for biochemical examinations. The results of these observations showed us the following facts:

- The gastric mucosal preventive effects of PGI_2 appear earlier (from 0 to 15 minutes), and β-carotene-induced gastric mucosal effects appear later (from 15 to 60 minutes) after the administration of necrotizing agents in both acid-dependent and non acid-dependent experimental models;
- The increased ATP–ADP transformations by membrane ATPase were obtained in the gastric fundic mucosal tissue (in association with the decreased extents of ATP–cAMP transformation) by both PGI_2 and β-carotene. These changes in the biochemical parameters of gastric fundic tissues were dose dependent and these appeared at the time of detectable characteristics of gastric mucosal preventions;
- The changes in the parameters of oxygen free radicals also were well detectable; however, the changes were not found to be dose-dependent actions.

We concluded the following from these observations:

a. There is a close and mathematically significant correlation between the protection of gastric mucosal damage by both PGI_2 and β-carotene and the changes in the biochemical parameters of membrane-bound ATP-dependent energy systems (with respect to extents in their changes and appearance in time). These correlations between the above-mentioned parameters were not dose-dependent and mathematically significant;

b. No differences were obtained in the appearance of gastric mucosal damage caused by acid-dependent (0.6 M HCl) and non acid-dependent (96% ethanol) mucosal damage, and their mucosal protective actions caused by a non scavenger (PGI_2) and a scavenger (β-carotene) have the same characteristics in these animal models;

c. The preventive actions of scavengers against tissue injuries involve significant changes in experimentally measurable parameters of oxygen free radicals; however, we suggest that the changes in the membrane-bound ATP-dependent energy systems have key roles in the development of tissue protective effects;

8. Selye (1936) emphasized the non-specificities of different stress reaching the living organs. The reactions of target organs give specific replies.

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We noted the results of the observations with 0.2 M NaOH, 25% NaCl, 96% ethanol and 0.6 M HCl (given orally), in the study of the development of mucosal damage, its biochemical background (Figures 181–183) and the development of prostacyclin-induced gastric mucosal damage (Figures 193–199). These results also clearly indicate its principal role and its action of stress theory established by Hans Selye (Szabo et al., 2012);

9. The epinephrine model offered a very special experimental opportunity to understand the possible action of one mediator (epinephrine) under different functional states of the target organ (target organ with different functional states). The epinephrine inhibited the development of gastric acid secretion and ulcer development in 24-hour pylorus-ligated rats; however, the epinephrine (given is in a suitable dose) at 4 hours later after pylorus ligation produces ulcer development. The biochemical background of the significant actions of epinephrine depend on the actual levels of membrane-bound energy systems, that is, the tissue level of ATP is normal immediately after pyloric ligation (therefore epinephrine produces a significant increase in the tissue level of cAMP); however, it was impossible at 4 hours after pylorus ligation when the tissue level of ATP was extremely low, and consequently the epinephrine application was not able to produce an increase in the tissue level of gastric fundic mucosal level of cAMP.

These results concluded the following:

a. The functional and regulatory steps of the feedback systems between the Na^+–K^+-dependent ATPase and adenylate cyclase systems work in a regulatory manner in the gastric tissues;

b. The regulatory mechanism, between the Na^+–K^+-dependent ATP and adenylate cyclase systems can be separated in some way under pathological conditions.

10. The results of animal experiments clearly indicated that the biochemical components differ significantly in the glandular stomach in comparison with the values measured in the forestomach (Mózsik et al., 1967 a, b, 1969 a, b, c, d; Mózsik et al., 1970). When we analyzed the time sequence and biochemical changes of the development of gastric hyperacidity and ulcer, in 24-hour pylorus-ligated rats, it was found that the gastric hyperacidity developed before ulcer, and the changes in the gastric mucosal biochemistry in both parts of the stomach appeared before the development of gastric hyperacidity(Mózsik and Vizi, 1976 a, b).

A significant biochemical gradient was biochemically proved in the gastric fundic, antral, duodenal and jejunal mucosa dependent on the gastric secretory responses (BAO, MAO) (Mózsik et al., 1976 a, b, 1979 a, b, c, e, f, g, h, 1981e).

The presence of tissue hypoxia was proved by Menguy et al. (1974 a, b, c) and Menguy and Master (1974) by hemorrhagic shock (Kitajima, 1989; Pihan et al., 1989). Pihan et al. (1989) explained the stasis of blood flow after the administration of chemicals. Under our experimental conditions, we could not prove the presence of tissue hypoxia (no elevation was obtained in the tissue levels of lactate, and the extent of phosphorylation was intact) (Mózsik

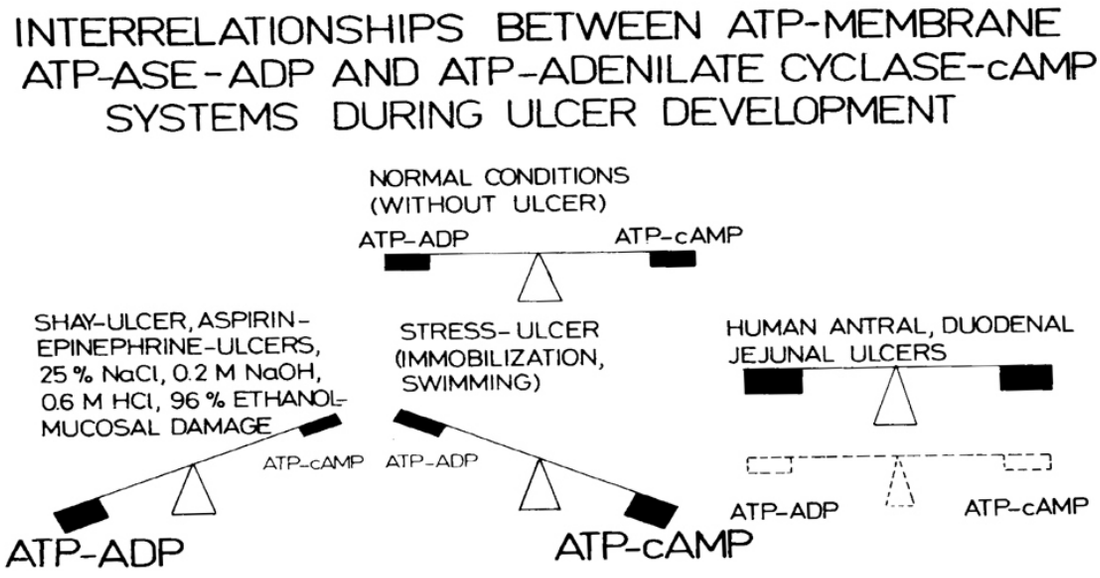

Figure 302. Changes in equilibrium between the ATP–ADP and ATP–cAMP transformations during the development of different experimental models (under significantly different experimental conditions). (For further details, see Chapters 7 and 8).

et al., 1971 a, b; Mózsik et al., 1979 b, f, h, 1981 e; Mózsik and Jávor, 1988e; Mózsik et al., 1990a, 1992c; Mózsik and Pfeiffer, 1992).

The application of biochemical–pharmacological methods in the peptic ulcer research offered a possibility to approach the developmental mechanisms (oxygen supply, biochemical changes, oxygen free radicals, vagal nerve, drug actions, scavenger actions, gastric mucosal secretory responses, ulcer development, drug-and chemical-induced GI mucosal changes) of aggressive and defensive factors in the GI mucosa. Our attention was dominantly focused on the actions of drugs acting at the mucosal level or efferent nerves. These studies analyzed the tissue reactions and not the programmed death of cells (apoptosis). The definition of tissue reactions differs from that of apoptosis.

Modern observations deal with the cellular mechanisms of apoptosis (Bódis et al., 1998; Pai et al., 2000, 2002; Szabó et al., 1996, 1997 a, b, 2000; Szabo, 2004; Tarnawski and Szabó, 2001).

In the future, we need to keep the integrity of living cells, tissues, animals and humans. We lost this integrity by receiving a great deal of detailed information. Our studies dealing with the membrane-bound ATP-dependent energy systems offered an excellent possibility to understand the integrity of these energy supply systems from the point of physiology, biochemistry, pharmacology and pathology.

11. Probably one of the most interesting results was obtained in surgical vagotomy when we observed that the PGI_2-induced gastric cytoprotective effect disappeared after bilateral surgical vagotomy (Jávor et al., 1981; Mózsik et al., 1982). The results of these observations first proved that the intact vagal nerve is necessary for gastric mucosal defense (not only for the gastric acid secretion). Similar results were published by Miller (1983). Unfortu-

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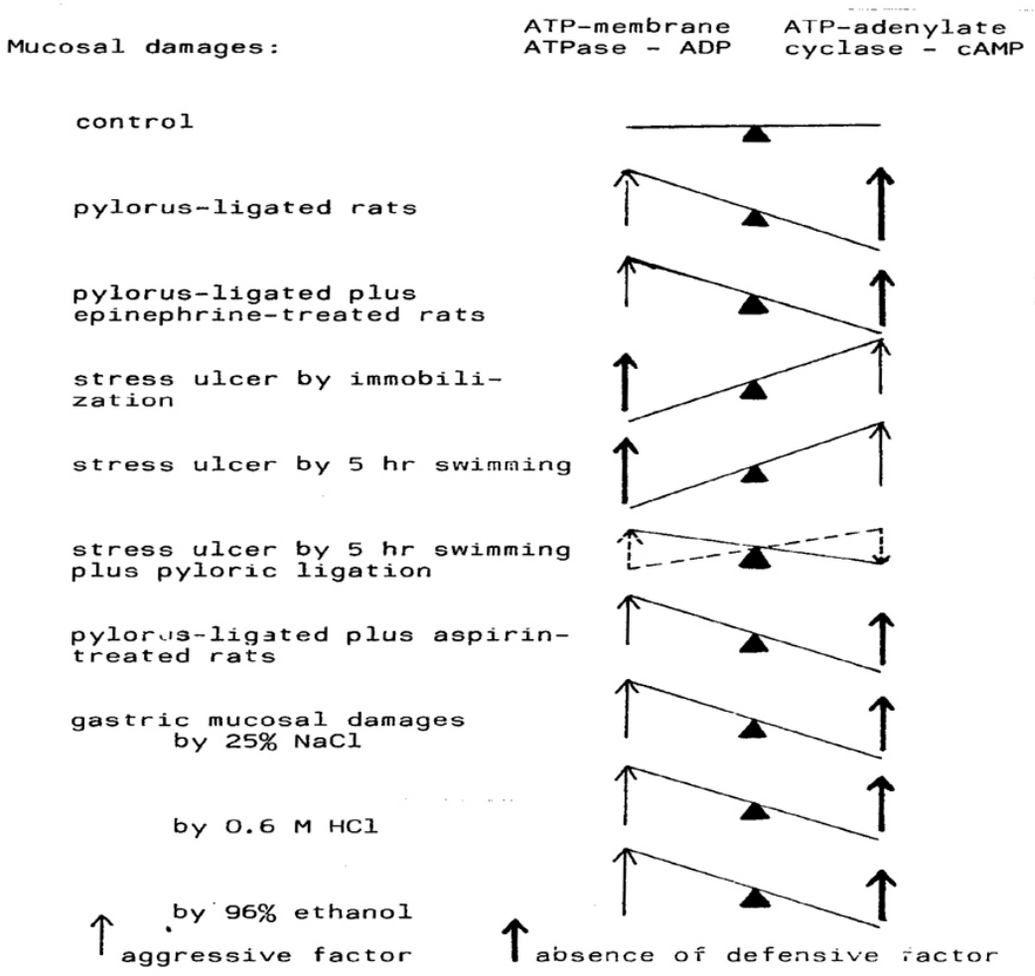

Figure 303. Correlations between the aggressive and defensive mechanisms during the development of gastric mucosal damage in different experimental models (a schematic summary of animal experiments). [Mózsik, Figler, Nagy, Patty, Jávor (1981). In: Mózsik Gy., Hänninen O., Jávor T. (Eds.) Advances in Physiological Sciences. Vol. 29. Gastrointestinal Defence Mechanisms. Pergamon Press, Oxford- Akadémiai Kiadó, Budapest. pp. 213–276 (with kind permission).]

nately, the necessary role of intact vagal nerve for the mucosal protection is known worldwide from the publication of Miller (we published this new observation earlier).

Later, Karádi and Mózsik (2000) studied surgical and chemical vagotomy (atropine treatment) in rats treated with indomethacin in detail, under different acute and chronic experimental conditions in the stomach, small intestine and large bowel. The indomethacin-induced mucosal damage (in the stomach and small intestine) enhanced after surgical vagotomy but not after "chemical vagotomy" (atropine treatment), and the small dose of atropine (cytoprotective effect) disappeared after surgical vagotomy.

Similar results were demonstrated with atropine, cimetidine, PGI_2 and β-carotene due to their failures in gastric mucosal protection after surgical vagotomy (see Section 8.17). The tissue levels of PGE_2 and PGI_2 (or its metabolite 6-keto-$PGF_{1\alpha}$) significantly decreased in the rat gastric mucosa after surgical vagotomy (see Section 8.17); however, we were of the opinion that these

facts (namely, decrease of PGE_2 and PGI_2) can only partially explain the disappearance of gastric mucosal protective effects of atropine, cimetidine, PGE_2, PGI_2 and β-carotene by surgical vagotomy (we emphasize better the roles of neural regulation of intact vagal nerve on cellular energy systems).

12. The actions of atropine, actinomycin D (inhibitor of RNA synthesis dependent on DNA), dinitrophenol (inhibitor of oxidative phosphorylation), epinephrine, histamine, mannomustine (Degranole^R) (inhibitor of *de novo* synthesis of DNA), pentagastrin, PGI_2, ouabain (specific inhibitor of Na^+–K^+-dependent ATPase enzyme) and tetracycline (inhibitor of protein translation) were studied and their dose–response curves were identified under three different experimental models, namely, in 4-hour pylorus-ligated rats (HCl secretion), ethanol-induced gastric mucosal damage and prostacyclin-induced gastric mucosal protection (see Section 8.14).

The affinity and intrinsic activity (α) curves were calculated from the obtained results (the doses of these drugs are given in [−] molarities), and the values of ED_{50}, intrinsic activity and pA_2 were calculated. These molecular pharmacological results are able to approach the importance of different subcellular mechanisms involved in the development of gastric acid secretion, ethanol- and prostacyclin-induced gastric mucosal damage in rats.

The results (including the values of ED_{50} and intrinsic activities and their pA_2 values) indicated practically the same results. It is tough to evaluate these results in understanding the cellular mechanisms of gastric mucosa under these experimental conditions.

13. The biochemical background of epinephrine ulcer (Section 8.15) clearly proved that the membrane-bound ATP-dependent energy systems (namely Na^+–K^+-dependent ATPase and adenylate cyclase) can be separated from each other depending on different functional states of target organs (Figures 263–267), which can give a schematic explanation for the gastric mucosal damage and prevention (Figures 302, 303). Similar conclusions can be drawn from the results of Figures 268–271.

14. The results of biochemical examinations in gastric mucosal tissues (in animals and humans) offered a general biochemical approach to the main biochemical cellular events (during the development and protection of mucosal damage). Changes in many mechanisms (at the levels of functions, cell membrane, mitochondrion, nucleic acids) are involved in these pathological and therapeutic processes of the mucosa of gastrointestinal tract.

There were and are many researchers who worked (or still working) on the study of gastrointestinal tract (pathologists, biochemists, physiologists, pharmacologists, internists, gastroenterologists, etc.) and they emphasized the importance of different fields from their research. An increased biochemical research has provided information on many cellular events in these target reactions, and we have to learn to evaluate the importance of these observations (dominantly done in animal experiments and isolated cells, cell lines).

The observation of the background of gastrointestinal mucosal damage and protection mechanisms shows that intact cellular energy systems are present in these processes.

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The results of our observations (done in humans and animals) show the key roles of membrane-bound ATP-dependent energy systems in different cell functions (under intact and different pathological conditions, without and with any drug treatments). These membrane-bound ATP-dependent energy systems also differ in the target organ under these investigational conditions.

We have described many observations in this book to understand different cellular reactions based on the key roles of membrane-bound ATP-dependent energy systems in both gastrointestinal mucosal damage and protection of patients and animals.

The chemicals can enhance or cause injury to the gastric mucosa (Figure 304). So a well-defined, regulated and dynamic system exists between the positive and negative metabolic adaptations to different (physical, chemical) stress. Furthermore, the GI mucosal injury can be healed (or some to extent prevented) by the positive and negative influences of the mediators, hormones and drugs (see Sections 5.7.1. and 5.7.2).

The mediator-, hormone- and drug-induced regulatory functions depend on the affinity and intrinsic activity curves of the membrane-bound ATP-dependent energy systems. The most important scientific information can be obtained by the comparison of values of pD_2 and pA_2 (when the doses are expressed in molarities).

Figures 303 and 304 demonstrate the presence of an active metabolic adaptation of gastric mucosa in rats and patients to increased gastric secretory responses and to chemical loadings. This metabolic adaptation is directed to ATP–ADP and to ATP–cAMP transformation in the cell membrane (with mitochondrial ATP). These facts suggest the existence of equilibrium between the two enzyme systems. This equilibrium is regulated by mediators, hormones, drugs (as first messengers) and different intracellular events. The different steps of these regulatory pathways were analyzed by the studies conducted on different acute animal models.

The PUD development is an acid- and biochemical (energetic)-dependent active metabolic adaptation; however, both membrane-bound ATP-dependent energy systems are involved in this active metabolic adaptation. These results suggest that the acid-dependent "genuine" ulcers appear as consequence of exhaustion of the metabolic adaptation (Mózsik et al., 1979 a, b, d, f, h, 1981a, 1982 a, b, 1987 a, b; Nagy et al., 1976, 1978, 1981 a, b) (Figure 73). The existence of the extremely high metabolic adaptation excludes the presence of tissue hypoxia.

11.5. Direct cellular damaging effects of ethanol, indomethacin and *Helicobacter pylori*

In this chapter, freshly isolated gastric mucosal cells were analyzed and the results were obtained. The effects of different mucosal damaging agents (such as *Helicobacter pylori* cultures, ethanol, indomethacin) were studied at the levels of cell membrane, mitochondrion and DNA, when these agents were administered individually and in combination).

This chapter concludes that the *Helicobacter pylori* alone does not produce any damage at the levels of cell membrane, mitochondrion and DNA, and it will not change by the administration of indomethacin.

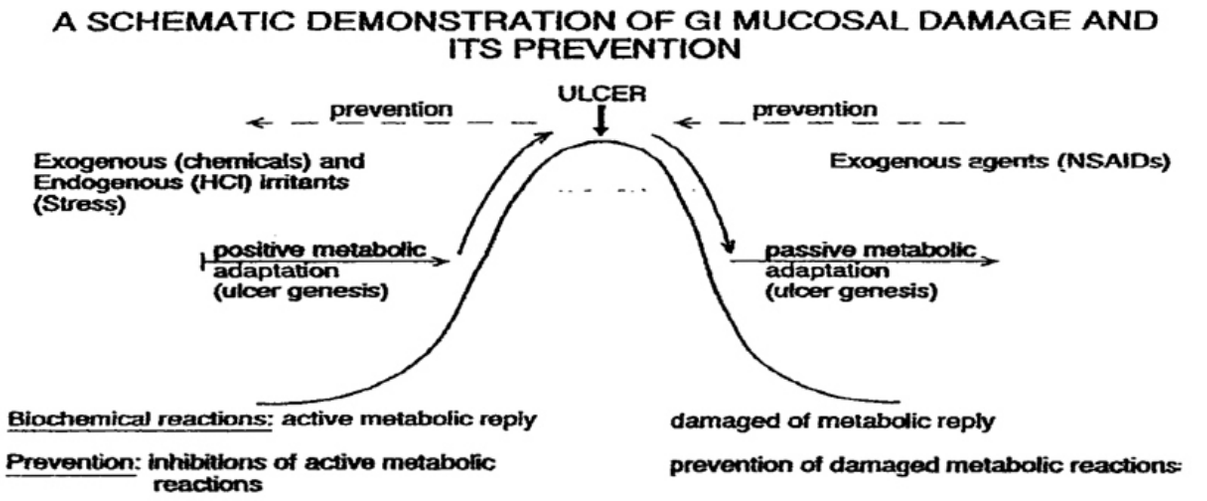

Figure 304. A schematic demonstration of gastrointestinal mucosal damage and prevention including human and experimental observations, summed from about 40000–50000 experiments. For further explanation, see Figure 303.

These results were surprising, because the presence of *Helicobacter pylori* in the gastric mucosa is the real cause for the development of peptic ulcer (gastric and duodenal ulcers) and chronic atrophic gastritis in patients.

The freshly isolated gastric mucosal cells are widely used to test the harmful and beneficial effects of different drugs (or drug candidates) in the experimental research of ulcer. It is well known that the rat (as experimental animal) is not the best experimental model to study and test the actions of *Helicobacter pylori* (see Chapter 9).

11.6. Observations with stable cell cultures

In earlier days, cell line cultures were widely available for research, because most of these cultures originated from human tissues. This fact suggests that the results obtained from these cell cultures are nearest to humans than those with rats (see Chapter 10).

The results of these observations were used to compare the results obtained from freshly isolated gastric mucosal cells and stable cell cultures. The mouse myeloma cell line is used as a "general cell line" in different fields of research, because this cell line has no secretory property.

The results obtained from these stable lines indicated different important notes to us:

1. The mechanisms of "cytoprotection" and "organoprotection" differ to some extent;
2. The freshly isolated gastric mucosal cells are more vulnerable than the stable cell culture lines against different chemicals (drugs, drug candidates);
3. The results obtained in the experiments with stable cell cultures can be accepted with a good criticism.

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11.7. General conclusions

It is very difficult to summarize the above-mentioned results (presented in the book). Furthermore, this study involves more serious work for clinicians than for people working just on experimental research. However, we have to mention a few points to explain this:

1. Patients with the same clinical diagnosis do not represent the same characteristics (such as their ages, body weights, life conditions, nutritional habits and states, genetics, etc.), whereas researchers have used the same animal strains (clearly identified their body weight, nutritional state, standard living conditions, genetic background, etc.);
2. The levels of clinical observations and animal experiments significantly differ from each other;
3. Clinical observations (exception of laboratory measurements from the blood samples) just can be done (owing many medical and ethical conditions and laws) in the before noon;
4. The conditions for carrying out clinical observations in human beings (patients) and animals cannot be compared to each other;
5. The clinicians know the borders of their knowledge in the everyday medical practice, but they practically are not able to carry out different research steps to solve these problems;
6. The clinicians do not have enough knowledge (from the modern biological research methods) and suitable conditions to carry out modern medical observations (exceptions are the clinical methods which depend on the modern diagnostic equipment, and these can be used for modern human research);
7. The fields of clinicians and researchers vary, and they have different conditions to do a well-planned research;
8. The clinicians have no correct information on the onset of diseases;
9. The fields of experimental research (in some meaning) are different from the problems of clinicians, and furthermore there are no collaborations between them;
10. Clinicians have consider important results of multiclinical, randomized, prospective, studies in their everyday medical practice (which somewhat depends on business), and there is no possibility to evaluate the background of clinical problems in patients' service;
11. General information (TV, radio, newspapers, Internet) on the so-called new observations are given by researchers (who are as far from the reality of clinicians and patients), and they are not participants in clinical realizations of experimentally discovered results (including the required time, economical support, etc.).

Earlier, it was an excellent practice for young physicians to learn more on the possibilities of methodologies (including new methods, general research laws, laws of presentations, etc.) when they stayed for years in research institutes before and after entering clinical practice. They learned much from the research institutes (e.g., the ways to approach different scientific problems). The postgraduate education offered an excellent possibility for them to recognize

the main problems of clinical practice (especially the details of medical treatments) and to plan the possibility pathways to scientifically approach them.

The authors worked as internists; however, they worked for 2–3 years in research institutes (in Europe and USA).

The following topics in the human and experimental research were:

1. We participated (as pioneers) in establishing the human clinical pharmacology in patients with peptic ulcer. This methodology offered us to do comparative clinical pharmacological studies of different drugs, to demonstrate the existence of drug tolerance (to the drug used chronically in the treatment of patients and to other chemically similar drugs that were not used in the treatment) together with the development of "pharmacological denervation phenomenon" in peptic ulcer patients – during a chronic drug therapy – however, these noted (proved) pharmacological observations disappeared in 6–10 days after cessation of drug therapy. These studies were carried out in the 1960–1970s, when we had the opportunity to use parasympatholytic drugs in the treatment of peptic ulcer.

Many observations were made later by us, which indicated that the surgical vagotomy was a harmful medical intervention in the treatment of patients with peptic ulcer. Many of our results clearly proved that the long-lasting effects of surgical and chemical vagotomy differ significantly in the gastric mucosa. It is important to note that "chemical vagotomy" can produce reversible pharmacological actions (development of tolerance to the medically used drug with "pharmacological denervation phenomenon") during the medical treatment of patients with peptic ulcer. The results of these observations proved clearly that the efficiency of the therapeutically used drugs decreased, and the complaints of patients increased during that time; however, these pharmacological effects can be reversed by the interruption of drug treatment (for 6–10 days). In other words, the sensitivity (efficiency) of the drug to the target organ can be tested clinically and pharmacologically by the administration of drugs intermittently in a long-lasting medical treatment of peptic ulcer patients. In contrast to the effects of chemical vagotomy, surgical vagotomy produces the final effects (including the compositions of gastric mucosal damage, the significant actions of their extra- and intracellular regulatory mechanisms, disappearance of gastric mucosal defensive actions by drugs and scavengers, changes in the tissue preventive effects of scavengers, etc.) on the target organs.

We applied the results of our observations in the chronic intermittent atropine treatment of patients with peptic ulcers, and the number of surgical innervations decreased significantly (from 160–170 patients to 2–5 patients in 1-year period in our surgical department). We followed up these patients for 10 years. Surgical intervention was not necessary in these patients as there was no complication.

It is true that we were away from the scientific problems of chronic atropine treatment in peptic ulcer patients; however, we learned the general problems of medical treatment with different modern drugs.

2. We noted the theoretical contradiction between the effects of therapeutically applied drugs (all of them inhibited the active metabolic adaptation of gastric tissues, while the

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ulcer disease appeared as a result of hypoxemic mucosal damage) and their desired actions, but we were not able to solve this significant contradiction in peptic ulcer treatment.

These problems were not studied in detail by the actually and traditionally known pathways in the 1970s. We had no concrete knowledge on the biochemical background of the development of gastric mucosal damage and prevention in both animal experiments and patients. This was the reason why we tried to start with the biochemical examination of gastric mucosal tissues.

The preliminary results of our biochemical observations in the gastric mucosa clearly indicated that significant changes can be found in the biochemical components of cell membrane, mitochondrion, proteins and nucleic acids.

It was observed that the changes in the biochemical composition of peripheral parts of cells (cell membrane, mitochondrion) are much more higher than those in proteins and nucleic acids.

In the early period of our biochemical observation, there was no internationally accepted methodology to approach the changes in the mitochondrial functions in detail (energy-dependent processes).

3. The preparations of Na^+–K^+-dependent (transport) ATPase and adenylate cyclase were carried out in the rat and human gastric mucosa. We noted that the functions of these enzymes can be regulated by mediators, hormones and drugs. Furthermore, the ATP is a common substrate for both the enzymes in the presence of Mg^{2+}. A very complex intra- and extracellular feedback mechanism system was proved to exist between the Na^+–K^+-dependent ATPase adenylate cyclase system under normal (physiological) and different pathological conditions. The significant changes in the equilibrium of regulation of the feedback system (Na^+–K^+-dependent ATPase and adenylate cyclase) are deeply involved in both development and prevention of gastrointestinal mucosal damage in animals and patients.

4. The results of measurements of tissue levels of lactate and the calculation of "energy charge" [(ATP+05 ADP)/(ATP+ADP+AMP)], together with simultaneous measurements of ATP, ADP, cAMP and AMP, are able to exclude the presence of impaired oxidative phosphorylation in the gastrointestinal mucosal tissues in both animal experiments and patients with peptic ulcer.

5. The cellular mechanisms of surgical and "chemical" vagotomy significantly differ in the rat gastrointestinal tract. The intact vagal nerve is basically necessary for gastric mucosal protection produced by PGE_2, prostacyclin, scavengers (vitamin A, β-carotene) and drugs (atropine, cimetidine).

6. *Helicobacter pylori* alone and in combination with indomethacin cannot cause any damage at the levels of cell membrane, mitochondrion and DNA on freshly isolated gastric mucosal cells.

7. A cellular biochemical explanation was given to the development and prevention of gastrointestinal mucosal damage in different animal models and humans.

11.8. Present and future observations

In the last decade, we summarized and reviewed our results obtained from our animal experiments and human observations for some actual scientific problems in different fields of biochemical pharmacological results (Mózsik, 2006), oxygen free radicals, antioxidants (Szabo et al., 2014) and role of *Helicobacter pylori* in the development of peptic ulcer disease in patients (Mózsik et al., 2014).

The actions (effects) of capsaicin on the gastrointestinal tract of animals since 1980 (Mózsik et al., 1997) and healthy human subjects and patients with different gastrointestinal disorders since 1997 were studied, with permission from the Hungarian Pharmaceutical Institute and Regional Ethical Committee of Pécs University (Hungary) since 1997 (Mózsik et al., 2009). These results clearly proved that the capsaicin (given in small doses) protects the development of gastrointestinal mucosal damage via the capsaicin-sensitive afferent nerves. These studies were conducted in collaboration with different institutes (Department of Pharmacology and Pharmacotherapy, Institute of Pharmaceutical Chemistry, Pécs University, Hungary) and therapeutic departments (Department of Gastroenterology, Petz Aladár Teaching Hospital, Győr, Department of Gastroenterology, Markusovszky Teaching Hospital, Szombathely, Hungary).

We observed the animal, preclinical and human examinations with capsaicin for innovative pharmacological and pharmaceutical research (since 2005).

We analyzed in detail the actions of different doses of capsaicin in animal experiments and stimulatory (small) doses on capsaicin-sensitive afferent nerves in healthy human beings and patients with different gastrointestinal disorders, principal problems of capsaicin chronic toxicology, preclinical dossier, basic problems of clinical pharmacology of capsaicin (tolerability, presence or absence of desensitization of afferent nerve to capsaicin during a chronic treatment), international (and national) permission of therapeutically (orally) applicable natural capsaicin preparation, classical clinical pharmacological phases I and II in order to produce new orally applicable drugs or combination of drugs in patients. These results were summarized and published recently (Szabo et al., 2012; Mózsik, 2014, Mózsik et al., 2014 a, b, c). Capsaicin-containing drugs are used alone or in different combinations in healthy human beings and patients with different gastrointestinal disorders.

12. Epilogue

The authors of this monograph are internists, who have been involved in various researches (physiological, pharmacological, molecular biological), from Hungary and other foreign countries (Norway, USA) either before or after becoming internists, gastroenterologists or clinical pharmacologists.

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The authors have focused on various aspects (including symptomatology, suggested etiologies, pharmacological and dietetical treatments, endoscopy and follow-up of patients for a long time period) of peptic ulcer disease, since the 1960s. Our knowledge, of course, has changed significantly from time to time in the above-mentioned fields. We joined the clinicians with some research questions (problems) in the field of peptic ulcer disease.

The clinical research study was conducted dominantly by surgeons in the first part of the last century. The possibility of surgical treatment of patients with peptic ulcer was emphasized dominantly by Germanian surgeons in the last part of the 19th century.

The use of different experimental (animal) models has internationally appeared to understand and approach the various problems (such as etiology, development mechanisms at different levels, prevention or treatment) of human peptic ulcer disease in the second half of the 20th century.

Professor Carl. C. Pfeiffer (Philadelphia, USA) was the pioneer researcher who organized an international workshop on peptic ulcer (in connection with the 4th World Congress of Gastroenterology) in 1970 at Copenhagen, Denmark. This workshop offered the "last opportunity" for the personal meeting of world famous (though older) researchers with the representative members of young generation. This workshop was named later as the "First International Conference on Experimental Ulcer" (Pfeiffer, 1971).

Following this conference, an international series of conferences on experimental ulcers has been established [Cologne (Germany), 1972; Parádfürdő (Hungary), 1976; Tokyo (Japan), 1980; Boston (USA), 1985; Jerusalem (Israel), 1988; Berlin (Germany), 1991; Kyoto (Japan), 1994; Hong Kong (China), 1997; Budapest- Pécs (Hungary), 2000; Dubrovnik (Croatia), 2003; Osaka (Japan), 2006; Split (Croatia), 2009; Tokyo (Japan), 2012 and the forthcoming conference will be located at Ottawa, Canada (2015)].

The Standing Committee of International Conference on Experimental Ulcer was officially established in 1976 [(C.J. Pfeiffer (Blackburg (USA) general secretary; members are T. Gheoghiu (Cologne, Germany), Gy. Mozsik (Pécs, Hungary), A. Robert (Kalamazoo, USA) and S. Umehara (Tokyo, Japan)]. One of the authors (Gy. Mozsik) was a member of the Standing Committee up to 2000, and he was general secretary of the Standing Committee from 2000 to 2009) (for details, see Mózsik 2006)].

Other series of international conferences (symposia) were established in connection with International Union of Pharmacology (currently with the name "International Union of Pharmacology, Basic and Clinical Pharmacology"). The Gastrointestinal Section of International Union of Pharmacology (GI Section of IUPHAR) was officially established in 1994 at Montreal, Canada. Before that, different satellite symposia were organized in connection with World Congress of Pharmacology (International Union of Pharmacology) in 1984 in London (UK), in 1990, in Amsterdam (the Netherlands) and in Pécs (Hungary) (1984, 1990). After the official establishment of GI Section of IUPHAR, special symposia dealing with GI pharmacology were incorporated in the program of main congresses [Munich (Germany) 1998, San Francisco (USA) 2002, Beijing (China) 2006, Copenhagen (Denmark) 2010, Cape Town (South African Republic) 2014; different satellite symposia were also organized in these main world

congresses of pharmacology [Pécs (Hungary) 1998; Honolulu, Hawaii (USA); Osaka (Japan) 2006]. Some other symposia of GI Section of IUPHAR were also organized in different parts of the world [Pécs (Hungary), 1995; Sperlonga (Italy), 1996; Kyoto (Japan) 2004; Honolulu, Hawaii (USA) 2012; Zagreb (Croatia), 2013; Budapest (Hungary), 2014].

One of the authors (Gy. Mozsik) was one of the establisher experts, member of different committees, the President (2002–2026) of the GI Section of IUPHAR and, of course, he organized several symposia in Hungary and other countries (see for details, Mozsik, Szabo, Takeuchi, 2006).

During the last four decades, we participated in establishing the processes of different international congresses:

1. Cell/Tissue Injury and Cytoprotection/Organoprotection in the Gastrointestinal Tract;
2. World Congress on Inflammation, Antirheumatics, Analgetics, Immunomodulators [Venice (Italy) 1984; Monte Carlo (Prinicipality of Monaco) 1986 and 1989; Geneva (Switzerland) 1995];
3. International Symposia of International Brain-Gut Society (Lake Arrowhead (Los Angeles) (USA) 1988; Pécs (Hungary) 1990; Florence (Italy) 1993; Pécs (Hungary) 1996)] (two symposia of this series were organized by Hungarian experts);
4. The First International Symposium on Gastrointestinal Cytoprotection was organized (established a new international series in this field) by Gy. Mozsik at Pécs (Hungary) in 1983, thereafter in 1987, 1991, 1995 and 2000;
5. World Congress of International Union of Physiological Sciences (Budapest, Hungary, 1980).

Summarizing our participation in the international flow of sciences, it can be interpreted that we tried to build up a functional bridge between the members working in Western countries and in Eastern (Central) European countries in the time period 1970–1995. This work was very difficult, but we believed that our work would result in a successful interaction between Western countries and Eastern (central) European countries in the field of scientific organizations and hopefully in their scientific activities. During that time, one of the authors (Gy. Mozsik) was the head of the First Department of Medicine, University of Pécs, Hungary (from 1993 to 2003), and his pupils spent approximately 51 years studying in foreign laboratories. We are proud that all colleagues who worked in Western countries returned to Hungary after finishing their research/study period.

Finally, we would like to summarize our scientific activities in the field of gastrointestinal research (focused mostly on peptic ulcer disease). We present this retrograde review of five decades starting from the 1960s; however, different observations and research were done in different clinical, instrumental conditions and research conditions. Consequently, we had to consider the actual time, when we made those observations and to give these critical (but, in some meaning, subjective) evaluations on our scientific activities.

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12.1. Clinical pharmacology of parasympatholytic drugs in patients with peptic ulcer

In the 1960s, the efficiency of medical treatment of patients with peptic ulcer was analyzed. The physicians had no objective methodology for the critical evaluation of efficiency of medical treatment of patients with peptic ulcer hade success of medical treatments ofpatients with peptic ulcer wereapproached only by the "subjective" signs of patients (to follow the changes in patients' complaints, body weight, appetite, etc.). These observations were given by the retrospective notes of the above- mentiond parameters.

The treatment of patients with peptic ulcer was done partly by internists (the so-called conservative treatment) and by surgeons. The indications for gastric surgery were dominantly based on the failure of medical treatments, which was one of the most important standpoints to us, the reason why we wanted to know more (in detail) about medical (pharmaceutical) treatments.

One of the most important questions was how to obtain objective data on the gastrointestinal absorptions of various drugs. Only the parasympatholytic drugs (atropine, scopolamine and some other tertiary and quaternary ammonium compounds) were used in clinical practice to decrease the suggested gastric acid hypersecretion.

No chemical methodology was found in clinical practice for the determination of parasympatholytics from different biological samples (serum, urine, bile) of treated patients. The biological methodology was used in our studies for the determination and measurements of different parasympatholytic drugs (in different biological samples) in patients treated with orally and parenterally applied doses of various drugs (see Chapter 2.).

The parasympatholytics (as water-soluble compounds) are not linked to albumin in the serum of patients; consequently, these compounds are excreted in the urine (after some metabolic processes) at the time of administration during the medical treatment. The liver (as the main metabolic organ) was suggested for the metabolization of drugs; so the results of this metabolic process could be followed by the detection of these drugs in the bile.

When the same dose of different parasympatholytics was applied orally and parenterally, we were able to identify the ratio of oral/parenteral dose of the drugs in the same patients. These results offered to control the suitable laws on the applicability of the "experimental pharmacology" in human medical treatment (no similar observations were carried out before in patients).

After careful systematic results from parasympatholytics in patients with peptic ulcer offered us to establish a "complete methodology for clinical pharmacology of parasympatholytics" in peptic ulcer patients (in 1960–1970), we received the possibilities for the identification of the following clinical pharmacological parameters:

a. Absorption from the gastrointestinal tract;

b. Ratio of oral/parenteral rate of different drugs;

c. Linkage of drugs to albumin;

d. Time course of drug actions by their urinary excretion;

e. Changes in the serum levels of different drugs during administration of different drugs.

These observations clearly indicated the following:

1. Different parasympatholytic drugs (dominantly quaternary ammonium compounds) are not absorbed from the gastrointestinal tract in patients with peptic ulcer;

2. The challenge of pharmacologists (namely to discover more new quaternary ammonium compounds to obtain longer blocking effects on the peripheral nervous system under experimental conditions) would help in clinical medicine (from the viewpoint of clinical pharmacology);

3. The failure of medical treatment (by quaternary ammonium compounds) does not give a real indication of gastric surgery (since these compounds are not absorbed from the human gastrointestinal tract).

12.2. Problems of chronic parasympatholytic drug in patients with peptic ulcer: Development of tolerance to drugs and together with appearance of "pharmacological denervation phenomenon" in patients with peptic ulcer

The decrease of gastric acid secretion was the main goal of medical treatment in parasympatholytics (in the 1960s) during a chronic (in about 4 weeks) treatment.

Systematic clinical observations were made in patients with chronic duodenal ulcer during chronic atropine treatment (4 weeks), when the gastric acid secretory responses (basal and secretory answer to superluminal but submaximal dose of histamine) and the ulcer healing (controlled by X-ray examination) were studied before and after the medical treatment.

It was surprising that the ulcers healed in patients with chronic duodenal ulcer, while no changes (no decreases) were found in the gastric acid secretion before and after a chronic atropine treatment (of course, without acute administration of atropine) (Mózsik et al., 1965). We could not interpret these results at the time of completion of these observations, since the "key role of gastric hypersecretion" was not present in these patients in order to heal duodenal ulcer in patients. These results are absolutely contradictory to the internationally suggested etiological standpoint of ulcer development (and healing) in patients with duodenal ulcer.

The theory of "cytoprotection" (e.g., existence of the gastric mucosal protection without any inhibitory action on the gastric acid secretion) was discovered and named by André Robert (1979), based on animal observations. Consequently, the existence of cytoprotection ("ulcer healing action without any decrease in gastric secretion") was proved in patients with chronic duodenal ulcer in 1965.

The inhibitory actions of the same doses of atropine were measured (from the viewpoint of clinical pharmacology) in these patients with duodenal ulcer before and after a chronic atropine treatment. Atropine was intramuscularly given (so the changes in the absorption were excluded). The magnitudes of the inhibitory effect of parenterally applied atropine significantly decreased the gastric basal and stimulated (given superluminal, but submaximal dose – 0.5 mg – histamine s.c.) dose after chronic atropine treatment.

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Thereafter, as atropine was orally given (before and after a chronic atropine), its levels were measured in the sera, bile and urine in patients who had no changes in these parameters. We concluded from these observations that no changes are present in the absorption, metabolism and excretion of atropine (in case of oral application) in the treated patients, during a chronic atropine treatment.

The vagal nerve is partially involved in the innervation of human parotid gland. The extents of salivary secretion of parotid gland were studies, using a coaxial capsule, during an acute administration of atropine (given orally or parenterally), and the inhibitory time indicated the same time as the excretion of drug from patients (when the titration of atropine in biological samples was parallel with the measurement of salivary excretion). When we injected patients with different agents (such as acetylcholine, epinephrine and histamine) before and after a chronic atropine treatment, the excretion of the basic salivary secretion significantly increased to acetylcholine (but not to epinephrine and histamine). These results focused our attention on the development of "pharmacological denervation supersensitivity" during a chronic atropine treatment.

In other words, "tolerance to atropine" and "pharmacological denervation supersensitivity" to acetylcholine appeared in patients with duodenal ulcer during the chronic atropine treatment. These phenomena (namely the development of tolerance to atropine and "pharmacological denervation supersensitivity" to acetylcholine) existed only together (for details, see Chapter 2). It was important from a clinical point of view that both the tolerance to atropine and "pharmacological denervation supersensitivity" and the tolerance to acetylcholine disappeared in 6–10 days after cessation of atropine treatment. We were the first researchers to demonstrate the existence of the development of tolerance to atropine and the "pharmacological denervation supersensitivity" to acetylcholine during a chronic parasympatholytic treatment in patients with peptic ulcer. In consequence of our observation, we applied only the intermittent atropine treatment in the medical treatment in patients with peptic ulcer.

12.3. Comparative clinical pharmacology in patients with peptic ulcer

The methodology of clinical pharmacology offered us to carry out randomized, prospective, multicentric and comparative clinical pharmacological studies with different therapeutically applied drugs (as an actual clinical examination) in patients with chronic gastric and duodenal ulcer (for details see Chapter 2). These studies were carried out with the permission of Regional Ethical Committee of Pécs University, Hungary. Different objectives, laboratories and subjective parameters were noted during the treatment of patients with peptic ulcer. The changes in the ulcer sizes were also calculated in the examined patients (before 2 and 4 weeks of treatments).

The most important note was from these observations that vitamin A produced gastric ulcer healing effect that was not less than those produced by other antisecretory drugs.

Earlier we suggested these observations that the antisecretory effect of drugs played the key role in medical treatment; however, vitamin A is a classical scavenger biological molecule

(without any antisecretory properties). Consequently, the phenomenon of gastric cytoprotection exists in patients with chronic gastric ulcer.

12.4. General biochemical examinations in the rat stomach under different experimental conditions

General biochemical examinations of the gastric mucosa (and other parts) were done in animals with different experimental conditions (effects of surgical and chemical vagotomy in acute experiments and in chronic observations) (for details, see Sections 4.2 and 4.3). These results clearly indicated that the "surgical" and chemical" vagotomy produced significantly different biochemical changes in the tissues of rat stomach. The key roles of cellular energy systems have also been suggested from these examinations.

12.5. Membrane-bound ATP-dependent energy systems in the gastrointestinal mucosa in animals and humans

These studies opened an absolutely new avenue for us to study the biochemical mechanisms and their regulations by mediators, hormones and drugs (*in vitro* and *in vivo* observations) (for details, see Chapter 6).

The classical Na^+–K^+-dependent ATPase and adenylate cyclase enzymes were first prepared from rat and human gastric mucosa by us. The examination of these enzymes gave an excellent possibility to study critically the changes of the membrane-bound ATP-dependent energy systems in the gastric mucosal tissues.

These types of observations are especially interesting (and important), because the ATP is a common substrate molecule for both Na^+–K^+-dependent ATPase and adenylate cyclase in the presence of Mg^{2+}. The actual level of ATP is also a limiting factor for the functions of Na^+–K^+-dependent ATPase. The ATP level decreases by the functions of membrane-bound enzyme systems; however, ATP resynthesis can be obtained only under intact oxidative phosphorylation. The measurements of tissue ATP (*in vivo* observations) performed alone do not give a correct argument to prove or to exclude the presence of tissue hypoxia. This question is a basic problem in the ulcer development (under experimental conditions of patients).

The results of these observations proved the existence of a very complex regulatory (feedback) mechanism system between the Na^+–K^+-dependent ATPase and adenylate cyclase in *in vitro* and *in vivo* conditions by mediators, hormones, drugs and by the actual level of tissue ATP in the gastric mucosa. Furthermore, the function of Na^+–K^+-dependent ATPase can be modified by smaller concentrations of these compounds, in comparison with those of adenylate cyclase. It is also interesting and important to note that the regulatory actions of these regulatory compounds produce contradictory directions (stimulation vs. inhibition or inhibition vs. stimulation) on the Na^+–K^+-dependent ATPase and adenylate cyclase from gastric mucosal tissues. We have to emphasize the extents of energy liberation by the transformations of ATP into ADP, and ATP and cAMP also differ from each other in terms of energy liberation.

The ATP–ADP transformation by Na^+–K^+-dependent ATPase represents the first-line metabolic adaptation of the gastric mucosal cells to different influences (drugs, hormones, media-

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tors), while the ATP–cAMP transformation by adenylate cyclase indicates the secondary metabolic adaptation of the cells in the gastric mucosa. The term "second messenger system" has been defined by Sutherland, who received the Nobel Prize in Physiology (Medicine) in 1971 for the discovery of ATP–cAMP transformation by adenylate cyclase in liver slides.

12.6. Biochemical measurements in the gastrointestinal mucosa of patients with peptic ulcer who underwent gastric surgery for ulcer disease

The gastric partial resection (dominantly according to Billroth II intervention) was frequently applied in the treatment of patients with peptic ulcer, because of the failure in "medical" (pharmacological, dietetic) treatment carried out by internists.

We never emphasized the importance of surgical treatment of peptic ulcer because we observed many early (dumping syndrome, diarrhea, etc.) and late (malabsorption syndrome, osteoporosis, stump cancer) complications of gastric surgery. These medical problems led us to evaluate the reason(s) why the "medical treatment" failed in these (1960s) years. These facts stimulated us to start with the critical analysis of the problems of pharmacological treatment in patients with peptic ulcer, and the methodology of clinical pharmacology appeared in consequence of these facts. The number of patients with peptic ulcer was 160–170/year who underwent surgical intervention at the First Department of Surgery, Pécs University, Hungary; however, after our clinical pharmacological results were introduced into everyday medical treatment, the number of surgically treated patients with peptic ulcer decreased to 2–3 patients per year in a very short time.

The necessity of gastric surgery was not indicated by internists, but by surgeons. Our biochemical observations were carried out on the resecates of human gastrointestinal tract obtained during surgical intervention.

The gastrointestinal resecates (obtained after surgical intervention) were biochemically studied (for details, see Chapter 7). Our biochemical examinations (using the internationally accepted methodology during the first half of 1970–1975) were expressed in relation to 1.0 mg DNA (representing the same number of cells).

The Na^+–K^+-dependent ATPase differs from the H^+–K^+–ATPase (for details, see Chapter 5); however, about 50–60% of Na^+–K^+–ATPase is incorporated into H^+–K^+–ATPase. The H^+–K^+–ATPase is located only in the parietal cells of stomach, while the Na^+–K^+-dependent ATPase can be found in all types of cells. Interestingly, the ATP is a common substrate molecule for both enzymes. (Note: We have to emphasize that we had no possibility to measure the cAMP directly from the surgically obtained resecates of the GI tract of patients with peptic ulcer at the time of gastric surgery.)

The gastric basal (BAO) and maximal (MAO) secretory responses were used as objective parameters for the stomach (these observations were carried out before the surgical intervention).

The biochemical results obtained from the gastric fundic mucosa and ulcerated antral, duodenal and jejunal mucosa must be observed.

These results were very surprising, since they were the same (note that the results were calculated as 1.0 mg DNA). The levels of ATP and ADP were higher in the gastric fundic mucosa with increased gastric acid secretory responses (together with the increased activity of Na^+–K^+-dependent ATPase). The same results were obtained in the ulcerated antral, duodenal and jejunal mucosa (1.5–2.0 cm around to ulcer), while these parameters were significantly lower (in the same patients) in the non-ulcerated (control) antral, duodenal and jejunal mucosa. The increased level of tissue ATP can be obtained by the increased oxidative phosphorylation, while the increased splitting (turnover) of ATP into ADP can be found by the increased Na^+–K^+-dependent ATPase in these tissue specimens. These results gave clear evidence for the exclusion of the presence of tissue hypoxia (impaired oxidative phosphorylation) in the ulcerated antral, duodenal and jejunal mucosa in patients with antral, duodenal and jejunal ulcers.

If we carefully observe the biochemical structures of corpus (fundus), antrum, duodenum in patients with peptic ulcer, we can notice that different energetic and biochemical gradients are present between fundic, antral and duodenal mucosa in these patients.

After a very careful analysis of these results, we can suggest that the clinically detectable appearance of antral, duodenal and antral ulcer is a consequence of a very active (increased) metabolic process (and not of decreased tissue metabolism). The possibility of adaptation to increased metabolic processes is determined by the original biochemical and energetic structures of fundus, antrum, duodenum and jejunum in patients with peptic ulcer. These structures, of course, depend on the general activity (such as gastric secretory parameters) of the stomach in humans (patients with peptic ulcer).

There are some problems with the critical evaluation of the presence of tissue hypoxia:

a. The decrease in gastric mucosal blood flow measured by different physiological methods does not prove the presence of tissue hypoxia in the ulcerated tissues in patients with peptic ulcer;

b. No clear and easily used methods were available in the case of humans (especially to measure the gastric mucosal blood flow (GMBF) in patients with peptic ulcer in time just before the development of ulcer);

c. The increased level of tissue level of lactate is one of the two main arguments to prove the existence of tissue hypoxia; the second one is the decreased tissue level of ATP due to impaired oxidative phosphorylation.

12.7. Messages of biochemical examinations in different ulcer models

Many animal observations were carried out to understand the changes in the gastric mucosa with and without mucosal damage and ulcer. A wide scale of biochemical methods were used in these animal studies (for details, see Sections 4.2 and 4.3) and different necrotizing agents (aspirin, indomethacin, ethanol, NaOH, HCL, concentrated NaCL solution and other drugs such as epinephrine, reserpine and stress situation) (or surgical intervention) were administered to cause gastric mucosal damage. The biochemical examination was done in a time-

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dependent manner after the administration of different necrotizing agents; consequently, we were able to study the biochemical mechanisms before the macroscopic appearance of gastric mucosal damage, and, of course, during the time of macroscopic appearance of gastric mucosal damage. The critical analyses of these results (obtained in different experimental models) helped in understanding the suggested key biochemical events responsible for the development of gastric mucosal damage (for details, see Chapter 8).

Our attention was focused on the changes in the members of membrane-bound ATP-dependent energy systems (e.g., ATP, ADP, AMP, cAMP) in connection with the measurements of tissue lactate levels in gastric mucosa. All biochemical measurements were carried out in the same tissue samples at the same time. The key goal was to understand the problems of tissue hypoxia in the development of gastric mucosal damage (in very different experimental conditions).

In other observations, we administered various drugs (atropine, cimetidine, drugs interfering with different subcellular mechanisms and vitamin A and β-carotene – as typical nutritional scavengers – prostacyclin) to prevent the development of mucosal damage produced by different chemicals or stress. The biochemical examinations were conducted under the same experimental conditions as those in the previous models.

We have concluded the following from the analyses of the results obtained from these biochemical examinations in different experimental models:

a. The ATP breakdown (by membrane-bound ATPase and adenylate cyclase) increased practically in all models, with the exception of aspirin-induced mucosal damage and pylorus ligation by after surgical vagotomy).

b. The changes in energy systems in cells appear before the macroscopic appearance of gastric mucosal damage, while these changes in the cellular energy systems can be prevented by the administration of different mucosal protective agents in the same time period as in the case of the development of mucosal damage.

c. The existence of feedback mechanism can be proven in different experimental models, in terms of development of mucosal damage and prevention.

d. The presence of tissue hypoxia can be excluded by biochemical observations in the gastric mucosa with the development of gastric mucosal damage.

e. The mucosal protection by drugs and scavengers, or biological agents (such as prostaglandins), exists in animals only in conditions of intact vagal nerve, while the gastric mucosal protection ("cytoprotection") disappears after surgical vagotomy, but not in the case of "chemical vagotomy." Consequently, the "surgical" vagotomy and "chemical" vagotomy differ significantly from each other. We were pioneers, who demonstrated first that the intact vagal nerve is involved in the increase of aggressive factors in the stomach, because no gastric mucosal protection exists after surgical vagotomy.

f. The gastric mucosal protection produced by scavengers appears in pathways of the changes in parameters of oxygen free radical system (peroxidase, glutathione peroxidase,

superoxide dismutase, reduced glutathione, MDA) and in the parameters of membrane-bound ATP-dependent energy system (ATP, ADP, AMP, cAMP). Interestingly, the mucosal protecting effects of scavengers (vitamin A, β-carotene) produced dose-dependent changes in the membrane-bound ATP-dependent energy system but not in the parameters of oxygen free radicals. It is important to note that these actions are associated with the changes of membrane-bound ATP-dependent energy system and oxygen free radical system; however, without the biochemical presence of tissue hypoxia in the gastric mucosa (in both the time of development of gastric mucosal damage and prevention by scavengers).

g. The mucosal aggressive and protective effects of different drugs (or other compounds) depend on the functional states of effector organ (including their biochemical background). The observation of these facts is an important factor in the medical treatment by different drugs (compounds). The clinicians have enough information on the onset of the disease and functional states of effector organ. Observing these facts, probably, we can better understand the efficiencies of various therapeutic drugs, but these suggestions are also true in the case of mucosal producing drugs.

It is well known that these experimental models cannot be interpreted in human pathology without criticism; however, we received more information in this field from experimental ulcers.

12.8. Observations on freshly isolated gastric cells from the rat gastric mucosa

The special cellular biochemical examinations were carried out on gastric mucosal cells freshly isolated from gastric mucosa of rat (for details, see Chapter 9). These methodologies were able to demonstrate the cellular damaging effects of different agents at the levels of cell membrane, mitochondrion and DNA.

The effects of ethanol, indomethacin and sonicated *Helicobacter pylori* cultures (obtained from the cultured strains of *Helicobacter pylori* isolated from the gastric mucosa in patients with duodenal ulcer) were studied.

It was very surprising to note that sonicated *Helicobacter pylori* were given alone in doses of 10^8 to 10^6 germs/mL, indomethacin and its combination had no actions at any level of cell membrane, mitochondrion or DNA of freshly isolated cells (for details, see Chapter 9). This experimental methodology is internationally used to screen the cellular mucosal damaging and protecting effects of compounds.

One of the authors (Gy. Mozsik) observed that gastric cancer did not develop in patients, who originally suffered from the classical duodenal ulcer (from 1960 to 2014), without gastric surgical intervention (Mózsik Szabó and Czimmer, 2014). It is well known that most patients with duodenal ulcer are infected with *Helicobacter pylori*. We are of the opinion that the presence of *Helicobacter pylori* infection is only one of many causes, which are able to produce gastrointestinal mucosal damage. It seems that researchers have forgotten the results of classic GI research when the role of *Helicobacter pylori* became emphasized. However, we have to

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remember the possibility that the single isolated cells from rat gastric mucosa are not able to produce prostaglandins.

12.9. Experimetal studies with different compounds on the stable cell lines

The tendency of drug (and some meaning physiological) research with stable cell cultures significantly increased during the last decades. We also used different stable cell lines to study the effect of various chemicals on cells and to do some toxicological examinations (for details, see Chapter 10).

The results obtained with different compounds in stable cell lines are important; however, these effects are not the same as those in living organs.

12.10. The "Take Home Messages" from the authors.

Several different mechanisms (existing at different levels of living organisms) run parallelly beside each other during the development of damage and protection at the levels of organisms, organs, tissues, cells or different subcellular particles (besides the genetic control in the whole living organisms). The researchers have many possibilities to modify a separated mechanism from this extremely large number of mechanisms. We can prove some correlation(s) between the examined parameters versus different phenomena. We believe that we are right and we discovered some new mechanism(s) in our field. Other researchers are in the same position to discover the actually studied phenomenon versus main problems of results in the field, and they also believed that they discovered some other new mechanism(s). Unfortunately, these new results together are not able to help to understand the human medical problems.

We are not able to understand the deep mechanisms, when we observe the whole organism; however, as we observe the very small pieces of cellular and subcellular mechanisms, we might lose the whole organism. This contradiction is also permanently present between clinicians and basic researchers.

Our attention was focused on the existing cellular regulatory mechanisms in the biochemical changes of gastric (gastrointestinal in patients) mucosa in patients with peptic ulcer and gastric mucosa in different experimental models (including the different subcellular particles) under basic (normal and different pathological conditions, without and with the application of different biologically active compounds, drugs).

We have faced the actual challenges of peptic ulcer disease in patients, namely, critical evaluation of the efficiency of medical treatment, principal role of gastric hypersecretion in ulcer development in patients, establishing the human clinical pharmacology, biochemical constitutes of gastric fundic mucosa with different gastric acid secretory responses, the presence of hypoxia in the ulcerated antral, duodenal, jejunal tissues around the ulcer, other detailed biochemical mechanisms of gastric ulcer in the human gastrointestinal mucosa under different conditions (fundic, antral, duodenal and jejunal) and in tissues (with and without ulcer).

A wide scale of experimental ulcers has been applied (together with different experimental conditions). The main attention was focused on the changes of cellular energy (membrane-bound ATP-dependent energy) systems versus the presence of tissue hypoxia (the lactate levels were measured together with other biochemical examinations to prove/to exclude the presence of impaired oxidative phosphorylation in the gastric mucosal tissues). The observations were done at the time of development of damage and its protection by different chemical compounds (drugs).

Answers to our (main) scientific problems are the following in the last half of the century:

a. Without clinical pharmacology, we were not able to critically evaluate the efficiencies (and their background) of the drugs used in the treatment of patients with peptic ulcer. We obtained an excellent reconfirmation by the international clinical pharmacological research to pioneer our work in establishing methodology of clinical pharmacology in patients with peptic ulcers.

The established clinical pharmacology gave scientifically based observations to understand the different medical questions and compare the efficiencies of drugs (with different actions of mechanisms).

b. The key role of decrease of gastric acid secretion (by therapeutically applied drugs) is not necessary for the healing of gastric and duodenal ulcer in patients. In other words, the phenomenon of "cytoprotection" exists in patients with both chronic duodenal and jejunal ulcers.

c. The development of "development of tolerance" to parasympatholytic drugs together with the "development of pharmacological denervation phenomenon" is one of the clinical pharmacological explanations for the existence of "cytoprotection" in patients with chronic atropine treatment. This explanation was never given for the existence of "gastric (duodenal) cytoprotection" in patients with chronic gastric and duodenal ulcer. However, it is also clear that the "gastric cytoprotection" is an existing phenomenon in patients with chronic gastric ulcer (for details, see Chapter 2) (without this clinical pharmacological explanation, vitamin A has really gastric mucosal damage, but without its inhibitory action on gastric acid secretion).

d. The presence of gastric hypoxia in the ulcerated antral, duodenal and jejunal mucosa (e.g., of impaired oxidative phosphorylation) biochemically can be excluded in the presence of gastric antral, duodenal and jejunal mucosa around chronic ulcer in patients with chronic peptic ulcer (because the biochemical compositions of these ulcerated mucosal tissues are the same as those in the gastric fundic mucosa with gastric hyperacidity).

e. The successful preparation of Na^+–K^+-dependent ATPase and adenylate cyclase by us opened an absolutely new gate to study and understand the classic biochemical mechanism of the equilibrium between different parameters of cellular energy system (ATP, ADP, AMP, cAMP) under normal (intact) and different pathological conditions).

The axis of cellular ATP–ADP–cAMP–AMP–ATP breakdown by the membrane-bound ATPase splitting enzymes (membrane ATPase, adenylate cyclase),– ATP resynthesis (under

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intact oxidative phosphorylation), tissue levels of lactate, gastric acid hypersecretion, the development of gastric (gastrointestinal) mucosal damage (ulcer), intact vagal nerve, damaging and protective effects of different drugs, decrease of gastric acid secretion and the protection of GI mucosal damage cover the main topics of gastrointestinal physiology, pathophysiology and pathology in animals and humans. The obtained results in this axis can be critically evaluated in respect with the results of the above-mentioned cellular parameters.

The drugs (and other compounds) represent the "first messengers," while the intracellular mechanisms together indicate the details of "second (intracellular) mechanisms" in the cellular energy systems in both normal (intact) and different pathological conditions, without and with the application of any drug (compounds). We have to emphasize that the changes in the cellular energy systems are in very close correlation with other intracellular mechanisms (for details, see Chapter 5). The details of these different mechanisms presented by international experts (over the world) are related closely to this axis. Our molecular pharmacological examination with the drugs interfering with different cellular mechanisms clearly indicated that the functions of the levels of cell membrane, mitochondrion, protein synthesis, RNA and DNA are involved in the development of gastric acid hypersecretion, mucosal damage and mucosal protection produced by PGI2 and scavengers (vitamin A, β-carotene) (for details, see Section 8.12).

The actions of first messengers and their intracellular changes in the energy systems depend on the actual functional levels of target organ (including other intracellular mechanisms) at the time after the onset of different pathological (drugs) processes.

f. The existence of "gastrointestinal cytoprotection" and drugs produced by different compounds (scavengers, drugs, other compounds) disappears after surgical vagotomy; however, it remains intact in the case of "chemical vagotomy." This is a great criticism on the clinical application (practice) of surgical vagotomy in the treatment of patients with chronic peptic ulcer.

g. The results of the observations obtained from freshly isolated gastric mucosal cells and stable cells lines (gastric cancer, hepatoma, colorectal cancer, mouse myeloma) gave important scientific information for researchers (clinicians); however, it is also important to note that these results differ – in some meaning – from those obtained in living organs;

h. The observations with capsaicin (in respect to all of the very strict international laws of clinical pharmacology) offer a new pathway for the medical treatment of patients with peptic ulcer and for the prevention of drug-induced gastrointestinal mucosal damage by the stimulation of capsaicin-sensitive afferent nerves via the stimulation of capsaicin receptor (TRPV1) and liberation of different neuropeptides (calcitonin gene-related peptide, CGRP; substance P, SP; somatostatin; glycagon).

Newer research fields in gastroenterology, such as the research with capsaicin or newer neural mediators, opened a new window to further approach the mechanism of gastrointestinal mucosal damage and prevention.

The clinicians have followed the theoretical and practical advantages of clinical medicine with the simultaneous development of basic research. It has been very difficult for clinicians to maintain this position (we have tried to live two lives in the last half century). We were basically clinicians; however, apart from that we foray into the experimental research, thus accepting the actual scientific questions of basic research in gastroenterology.

There are general problems that no critical and scientific communications exist between the clinicians and basic researchers in gastroenterology.

The following list of references includes (incorporates) the most selective list of references, the detailed list of references is incorporated in the original publications.

Acknowledgements

The authors express their thanks to all Hungarian and Foreign coworkers.

These studies were supported by the grants of Hungarian Ministry of Health (ETT-735/93, ETT-03660/93, ETT-385/96, ETT-34/2000, ETT-595/2003), Hungarian Research Funds (T-307, T-2466, T-016945, T-020098) and National Office for Research and Technology ["Pázmány Péter programme" (RET-II 08/2005) and "Baros Gábor Programme" (REG_DKI_ O, CAPSATAB, 2009-2012)].

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