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Chapter

Introductory Chapter: From Adenosine Triphosphate to Basic and Clinical Research in Light of First and Second Messenger Systems to Cellular Energetical and Other Regulatory Functions of Cells in Animals and in Humans (with a Sample of Peptic Ulcer Disease Research)

Gyula Mózsik

1. Introduction

The living animals and human organisms, organs, and cells are in a good equilibrium under the normal conditions. This excellent equilibrium can be kept with a lot of regulatory mechanisms at the level of whole organisms, different organs, and different cells, which together can organize the different regulatory steps and pathways under normal conditions for the living organisms. These regulatory mechanism systems represent a wonderful world. That is the very simple explanation for that why many people do research works in these fields and they wanted to know more and more details about this wonderful world. The researchers are working in very different fields; however, all of us want to know more and more the essential and general laws of the different regulatory mechanism systems in hoping that these new observations will help us in keeping further this wonderful world in the forthcoming future.

The researcher people are biologists, bacteriologists, animal researchers, veterinary physicians, human physicians (and related specialists, like anatomists, physiologists, biochemists, pathologists, pharmacologists, basic researchers, clinicians, etc.), agricultural researchers, etc.

Basically we want to know more and more on the functions of living organisms; however, the possible approaching pathways are very different in the science; furthermore the "science" is a permanently changed process. Firstly, we try to register the reactions (answers) of the whole organism, including physical, physiological, and psychological aspects. In other words, we will see the whole organisms at the first time; however, later we want to know more on their mechanisms involved in the different "whole" reactions. Consequently, the main research tendency turned

into the microworlds from the whole organisms (e.g., biochemistry, pharmacology, etc.), and now we are at the levels just at the level a small particles of cells (like different enzymes, biochemical reactions, membrane functions, nucleic acids, and very special particles).

This book contains four (five) different excellent chapters, three of them on theories of health and diseases and one more chapter dealing with human clinical problems, which together give a nice overview on the theories of human medical practical problem.

2. First and second messenger systems

The centrally and peripherally originated neural influences (mediators), different hormones, and—during the medical treatments—different drugs reach in the serum the plasma cell membranes.

The terminology of cell membrane represents a very complicated system by using this terminology. A lot of different enzymes and receptors are located in the membranes with significantly different mechanisms (functions).

The different first messengers (hormones, mediators, drugs)—if they will not be inactivated in the serum—will meet first with the cell membrane, and they will modify the regulatory mechanisms in different extents.

The so-called sodium pump has been studied widely in the physiology. This "sodium pump" system was responsible for the keeping of equilibrium between the significant concentration gradients of sodium and potassium in the serum versus intracellularly.

There was no question that this process is an energy-dependent process; however, the details were not known.

The sodium-potassium pump was discovered by Skou (in Denmark) in the 1950s, and it was proved that this sodium-potassium pump is responsible for the so-called sodium pump (1965). The sodium-potassium pump can be worked by a membrane enzyme. This enzyme is located in the membrane, splitted the mitochondrial adenosine triphosphate (ATP) and presence of $Mg^{2+,}$ Na^{+} and K^{+}, and this process can be inhibited by application of g strophantin (ouabain). Skou (Aarhus, Denmark) was awarded the Nobel Prize of Chemistry in 1997.

Later Sutherland (who received the Nobel Prize of Physiology or Medicine in 2001) discovered the existence of adenylate cyclase enzyme. This enzyme is also located in the cell membrane, and the same electrolytes are necessary for the function as in the case of membrane ATPase.

Consequently, it became clear that the mitochondrial adenosine triphosphate is a common substrate for both membrane ATPase and adenylate cyclase.

The breakdown of mitochondrial ATP by membrane ATPase is adenosine diphosphate, while adenylate cyclase is cyclic adenosine monophosphate (cAMP). During these processes, energy will be liberated in the cells; however their extents are different from each other, namely, its value is about two times higher in the case of adenylate cyclase than in the case of membrane ATPase. The adenosine monophosphate is a common split intracellular compound after the breakdown of ADP and cAMP.

Atkinson (1968) created a formula to express the values of the actual tissue circumstances of phosphorylation/dephosphorylation by the following method: [(ATP + O.5 ADP)/(ATP + ADP + AMP)]. This value is equal to l, when all adenosine compounds are in the phosphorylate form, and this value is zero, when all adenosine compounds are in the dephosphorylated form. The application of this formula is very useful in different observation circumstances.

From these very short informations, our attention has been focused in our peptic ulcer research.

The second messenger systems are very complicated in our days, which are out of our present work.

The editor of this book is a physician (internist, gastroenterologist, clinical pharmacologist). However, before the editor would turn in the clinical works, he worked a cup of years in physiological and pharmacological (molecular and biochemical pharmacological) departments. When I met—as a physician—with the patients, I registered many difficulties in their everyday medical duties, namely, the patient's treatments, and before taking of good diagnoses.

3. Molecular biochemical observations in human peptic ulcer diseases

My clinical work started in a medical department at Second Department of Medicine, University of Debrecen, Hungary (1960). I met with a lot of gastroenterological patients, who originally suffered from "classic or genuine" peptic ulcer disease (PUD) (with and without gastrointestinal (GI) bleedings). We had very limited possibilities to take diagnosis (PUD) and treatments of patients with PUD in the 1960s; however, in the forthcoming 10 years, the fiberoscopes appeared, beside the X-ray examinations. The etiological role of tissue hypoxia was suggested in the development of gastroduodenal mucosal damage in association with the increased tone (activity) of the vagus nerve. In the different European countries, the patients received atropine treatment (three times/day in doses of 0.3–0.9 orally or 0.5–1.0 mg intramuscularly for 3–4 weeks). The scopolamine was used in the USA beside the atropine. Following the medical treatment, we believed that the patients healed, or we (internists) offered further the patient to surgeons for taking gastric surgery (partial gastrectomy or partly surgical vagotomy).

The increased gastric secretory acid secretion was believed to be in the background of PUD; however no objective method(s) was (were) in the hand of clinicians to measure the quantities of gastric acid secretion at that time. In the 1960s—near their end—different methods were established to measure gastric acid secretion (including the gastric basal acid outputs, BAO, and maximal acid output, MAO) using nasogastric tubes, and patients were given different doses of histamine or pentagastrin. Independently from the presence of these methods, practically these were not used generally in the everyday medical practice.

Many things (methods of clinical observations, modern endoscopic instruments) changed in the forthcoming time, and the basic pharmacological research produced a lot of tertiary and quaternary ammonium components (as antisecretory agents). The effects of these compounds were tested practically in animal observations, and these results were accepted by the clinicians and introduced into the medical treatment. The results differed in patients from those obtained in animal experiments, and in some cases no beneficial effect of used drug is obtained in patients. Between the years 1960 and 1970, a modern methodology was elaborated by us to objectively measure drug absorption, metabolism, excretion, serum levels of applied drugs, gastric acid secretory responses (BAO, MAO), parotid secretory responses, gastric motility, and gastric emptying. These results obtained in oral or parenteral application of different drugs offered a possibility to establish a complex clinical pharmacological methodology for parasympatholytics and for other drugs.

The human clinical pharmacology developed further as produced the necessary the controlled clinical pharmacological trials of different drugs. The first step was to prove that really the different drugs have any beneficial effect of the target organ. The identification and determination of drug action ("without giving any active

drugs") were one of the biggest problems (placebo effect) of the human medical therapy (some to up to now, the correct understanding of this problems represents an essential scientific and medical treatment problems) (like production of new potentially new molecule is the research medicine, and the same in the clinical practice). This problem is now out of our point of view in the practical every day medical treatments.

We had good opportunity to carry out enough human studies on PUD patients with different parasympatholytics, histamine H2 receptor blockings, antigastrin, and proton pump inhibitors (PPI), antioxidants, and scavengers (so-called cytoprotective agents, like vitamin A, beta-carotene).

Just a small explanation is needed to understand the following step in our research. The vitamin A and beta-carotene are both together, and these agents are essential participants of human nutrition; however, these compounds have no any inhibitory effect on the human (and animal) gastric acid secretion. These observations excluded, at least in some part, that only the gastric acid (HCl) secretion is a responsible etiological factor to the development of GI ulcer diseases. Our clinical pharmacological studies clearly indicated existence of this phenomenon of this factor in patients with duodenal and gastric peptic ulcer. It was also very surprising when we carried out regular treatment with atropine in duodenal ulcer patients, we found that the ulcers healed; however the gastric acid secretion did not change during the chronic treatment [1]; meanwhile the terminology of "cytoprotection" was introduced by André Robert et al. in 1979, and later this name was generally accepted worldwide.

Originally, we wanted to understand the etiological background of PUD and the details of our medical activities during the patients' treatments. We tried to analyze very carefully the many results of correct human pharmacological treatments, and we were not able to understand the "essential point(s)" of etiology of PUD and our treatments. Furthermore, if the presence of tissue hypoxia is important in the development of GI mucosal damage, then we have to go further in the determination of the direction of the quantities and changes of cellular energy storage molecule, namely, "adenosine triphosphate (ATP)," in the healthy and ulcerated GI mucosa. However it is also important that the determination of ATP alone is possible only with the biochemical markers of the cell reactions. Consequently, our attention forwarded to biochemical research profile. Perhaps, it is not needed to mention that this is an extremely big challenge for the physicians working in the everyday medical practice (as internists).

The measurement of ATP in the different GI mucosal tissues represents only the equilibrium between the breakdown of ATP and its resynthesis. The oxygenization of mucosal tissues is not necessary in the case of ATP breakdown; however energy will be liberated by this biochemical reaction. The liberated energy is necessary for the normal functions of the very different cellular events (active transport at the cell membrane, secretory responses of the stomach, protein synthesis, etc.). However, the ATP resynthesis is possible only in circumstances of well-oxygenized tissues; meanwhile if the statement is true that hypoxemic event is present in the ulcerated gastrointestinal mucosa, consequently the ATP resynthesis is a priori inhibited. We suggested at the start of our biochemical examinations that we will find these results in a later time.

We had another (but essential) problem at that time, namely, in patients with PUD, we use the drugs in medical treatment; all of them block the active metabolic processes at least in the human gastric fundic mucosa (decrease of gastric acid secretion). If this statement was absolutely true, then why is the application of different drugs inhibiting the gastric acid section useful for the healing of damaged mucosal damage? There was a *contradiction in objecto*.

From 1964, we started with the biochemical examinations of the stomach in animal gastric tissues and in human gastric (fundic, antral, and jejunal) mucosa obtained in resecates at human gastric surgery. We did biochemical extractions of acid-soluble inorganic and organic phosphates, phospholipid phosphates, ribonucleic (RNA), and deoxyribonucleic acid (DNA). These biochemical fractions of gastric tissues generally represented the main components of cells: lipid (as membrane), acid-soluble inorganic and organic phosphates (mitochondrion), RNA (partly the cytoplasm and well as nucleus), and DNA (nucleus). In other words, we tried to study the different compartments of gastrointestinal cells. It was important to note that at least 0.3–0.5 g wet tissue sample was necessary to carry out of the abovementioned biochemical extractions. Of course, more tissue samples were obtained in the different parts of the human stomach, and all biochemical extractions and the classical measurements were done at the same time. The results were calculated and expressed to 1.0 mg DNA. Classical histological examinations were done. The tissue samples from the human gastric (antral), duodenal, and jejunal ulcers (after Billroth II operation) were obtained from different distances to form the edge of ulcer. In a later phase, we were able to successfully prepare membrane-bound ATP-dependent enzymes, namely, the Na^+-K^{+-}ATPase and adenylate cyclase, directly from the gastric mucosa from rats and animals, and we received a possibility to study actions of different drugs on both enzymes, firstly in vitro circumstances, later in living organs in animal observations (of course). These results were critically summarizing in the last years [1–4]. (I used **Tables 1, 2** and **Figures 1–5**, together with the given information texts to these demonstrations, and used in the text the reference list number used in the original summary monography).

Drugs	**ATP-ADP transformation**			**ATP-cAMP transformation**		
	Effects	**Doses**	**(M)**	**Effects**	**Doses**	**(M)**
Acetylcholine	Stimulation	10^{-7} M	→	Inhibition	10^{-4} M	→
Parasympatholytics:						
Atropine	Inhibition	10^{-11} M	→	Stimulation	10^{-8} M	→
Isopropamide	Inhibition	10^{-8} M	→	Stimulation	10^{-5} M	→
Gastrixon	Inhibition	10^{-8} M	→	Stimulation	10^{-4} M	→
Epinephrine	Inhibition	10^{-9} M	→	Stimulation	10^{-7} M	→
β-blocker (Visken)	Stimulation	10^{-4} M	→	Inhibition	10^{-5} M	→
Histamine	Inhibition	10^{-11} M	→	Stimulation	10^{-8} M	→
Cimetidine	Stimulation(?)	10^{-4} M	→	Inhibition	10^{-6} M	→
Pentagastrin	Inhibition	10^{-11} M	→	Stimulation	10^{-9}	→
PGE_1	Inhibition	10^{-11} M	→	Stimulation	10^{-9} M	→
PGE_2	Inhibition	10^{-11} M	→	Stimulation	10^{-9} M	→
Ouabain	Inhibition	10^{-8} M	→	Stimulation	10^{-4} M	→
cAMP	Inhibition	10^{-13} M	→			

**Direct effects of the membrane-bound ATP-splitting enzyme activities.*

Table 1.
Pharmacological effects on the transformation of ATP into ADP by membrane ATPase and the ATP-cAMP transformation by adenylate cyclase from rat and human gastric, fundic, antral, duodenal, and jejunal mucosae [113] (with kind permission).*

Mediators	Actions	Affinity values (pD_2)	Intrinsic activities	
			(α)	(pA_2)
ATP-membrane ATP-ase-ADP				
Ach	Stimulation	5.50	1.00_{Ach}	5.50
Histamine	Inhibibion	9.70	$1.00_{Ouabain}$	9.70
Pentagastrin	Inhibibion	10.55	$0.87_{Ouabain}$	10.55
ATP-adenylate cyclase-cAMP				
Ach	Inhibition	5.30	$-0.70_{Pentagastrin}$	5.30
Histamine	Stimulation	9.30	$1.00_{Pentagastrin}$	9.30
Pentagastrin	Stimulation	9.40	1.00	9.40

Table indicates affinity (pD_2) and intrinsic activity (pA_2) curves for the actions of acetylcholine, histamine, and pentagastrin. This table also indicates the contradictory actions of these agents on Na^+-K^+-dependent and adenylyl cyclase systems.

Table 2.
Correlations between the magnitudes of drug actions on Na^+-K^+-dependent ATPase and the magnitudes of Na^+-K^+-ATPase activity prepared from the human gastric fundic mucosa.

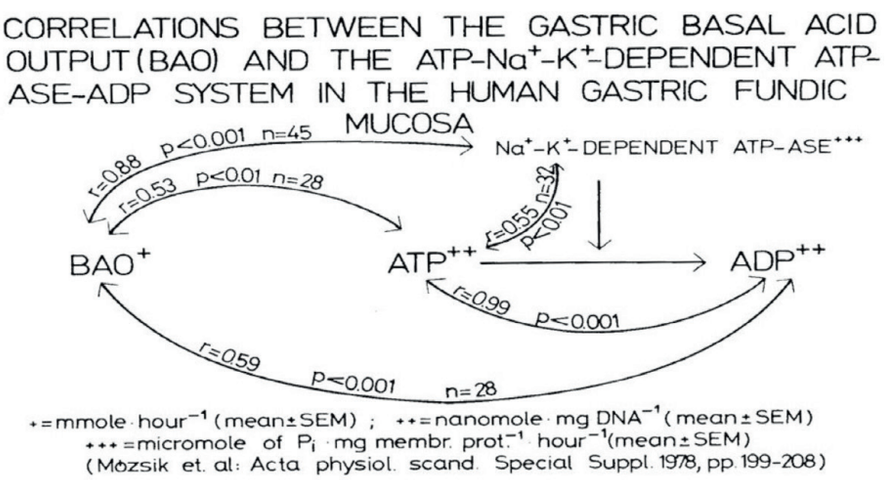

Figure 1.
Biochemically regulatory pathways between Na^+-K^+-dependent ATPase and tissue levels of ATP and ADP in the human gastric fundic mucosa on dependence of gastric BAO values (means ± SEM) [25] (with kind permission).

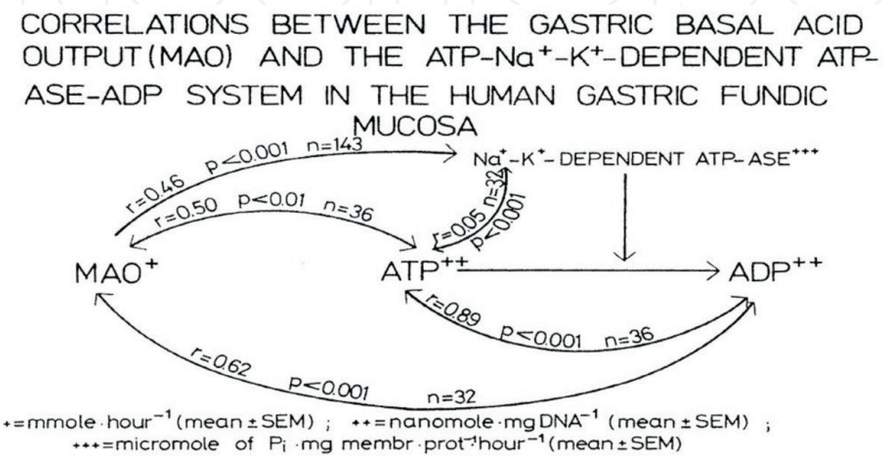

Figure 2.
Biochemically regulatory pathways between Na^+-K^+-dependent ATPase and tissue levels of ATP and ADP in the human gastric fundic mucosa in dependence of gastric maximal acid output (MAO) values [65] (with kind permission).

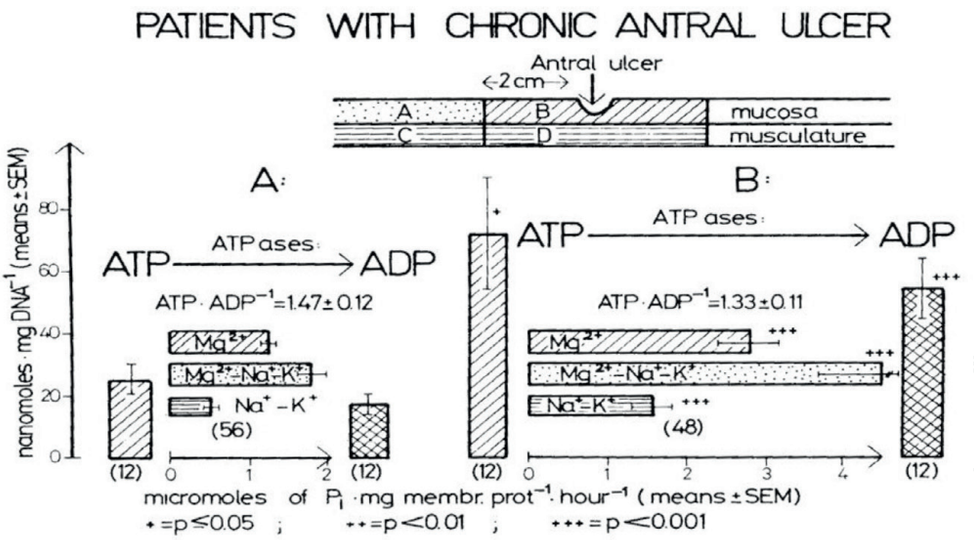

Figure 3.
Changes in the extents of ATP-ADP transformation in the antral mucosa of patients with chronic antral ulcer in the ulcerated and non-ulcerated (control) mucosae (means ± SEM) [127, 145] (with kind permission).

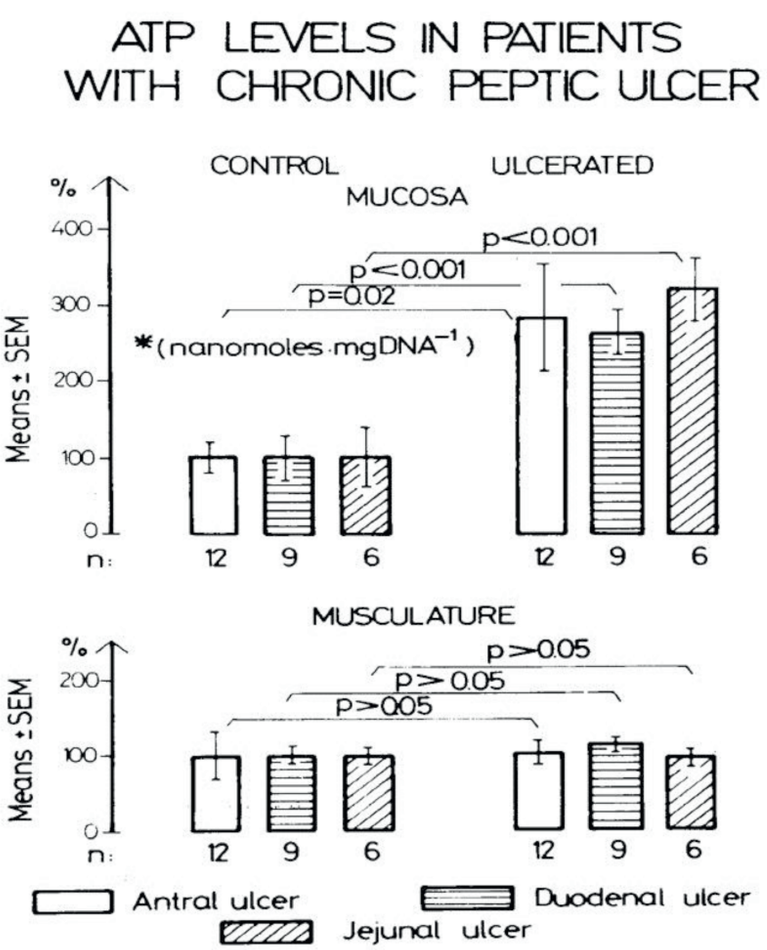

Figure 4.
Comparative demonstration in the changes of the tissue levels of ATP in the ulcerated vs. non-ulcerated antral, duodenal, and jejunal mucosae (the musculature located under the examined mucosa tissues) (means ± SEM) [143] (with kind permission).

There are some important notes from the clinical researchers and directions of basic researchers:

1. These types of biochemical pharmacological studies just are able to give an actual information (owing the human ethical positions, therapeutic protocols

used in patients' medical therapy, human rights). These problems are in the case of basic research also.

2. In animal models we really inform the provocation agents (we used 17 different models), and we used all the time a dose–response curve and followed the time-course events. All the biochemical examinations (from one animal) were done at the same time. The results were calculated. The applied agents were expressed in molecular weights, and the affinity and intrinsic values (curves) were calculated from the obtained dose–response curves.

3. The evaluation of the obtained results was evaluated at that time when the whole observations were finished.

4. These types of examination can be very hard work for clinicians.

5. I tried to demonstrate by my works how the clinicians are able to create a special bridge between the basic and clinical research works.

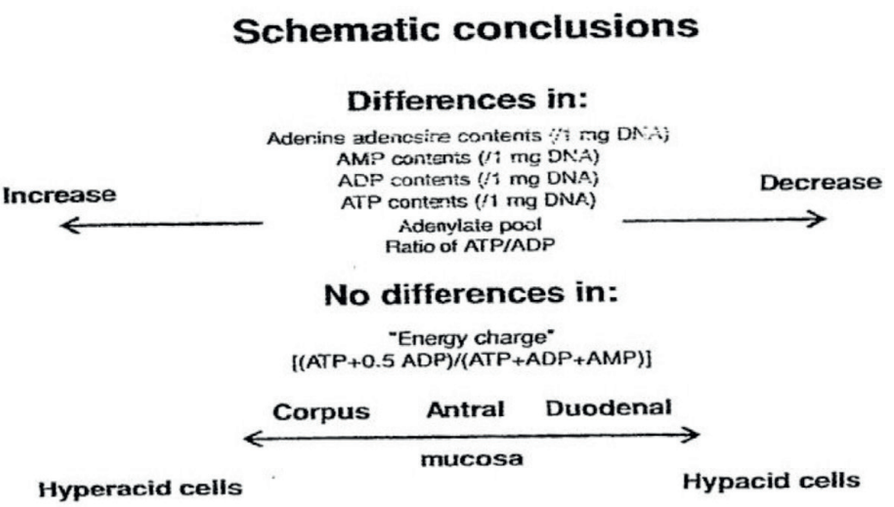

Figure 5.
The schematic presentation of biochemical buildup of human gastrointestinal mucosa in patients with different gastric acid secretory responses. All of the adenine and adenosine compounds increased significantly (meanwhile the stream of ATP breakdown enhanced in both directions) in the gastric corpus mucosa in comparison to those results obtained in the corpus mucosa of 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 mucosae. 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 [149, 150] (with kind permission).

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