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Theoretical Backgrounds of the Necessarity for the Changes of Paradigm in Our Ulcer Research

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After the active participation in the human clinical pharmacology of patients with peptic ulcer, we were not able to understand how the ulcer actually heals in the patients. Our problems pointed out the following results:

1. The gastric acid secretion [as basal secretion and stimulated secretion produced (provoked) by superluminal – but submaximal – dose of histamine] was unchanged during the medical treatment; however, the ulcer healed. We were not able to explain these contradictory results;
2. The results of clinical pharmacological studies (wide scale of anticholinergic agents) gave us a lot of new insight from the clinical pharmacological parameters (e.g., their absorption, metabolism, excretion) of clinically used drugs. We learned well that different therapeutically applied drugs a priori (e.g., Troparin, Gastropin®) will not absorb from the GI tract during the treatment; consequently, we were not able to find the beneficial effects of these drugs during the medical treatment;
3. The development of tolerance to atropine together with development of “pharmacological denervation phenomenon” has been proven in the background of unchanged gastric acid secretion in patients with duodenal ulcer, during a chronic atropine treatment (see chapter 2.2.). This newer clinical pharmacological explanation has been applied for “existence of gastric cytoprotection.” It is true that this phenomenon was observed in patients with duodenal ulcer in terms of the existence of “cytoprotection phenomenon” (not in animal experiments but in patients with duodenal ulcer);
4. When the existence of gastric mucosal protective effect was proved in animal experiments (Jávor et al., 1983), it was clear that vitamin A does not inhibit the gastric acid secretion.

Similar results were obtained in patients with vitamin A, for example, it does not inhibit the gastric basal acid (BAO) and maximal (MAO) acid outputs in healthy subjects (Morón et al.,

1984); however, it prevented the indomethacin-induced gastric mucosal damage in healthy human subjects (Mózsik et al., 1986).

The results of our randomized, prospective, multiclinical and multicentered studies in patients with chronic gastric ulcer clearly proved that the chronic gastric ulcer really heals without any decrease of gastric acid secretion (Patty et al., 1982; 1983). In other words, we also proved the existence of gastric “cytoprotection” in patients with chronic gastric ulcer.

The vitamin A is a typical scavenger and nutritional molecule, and we used the name of “nutritional gastrointestinal cytoprotection” for animals, healthy human subjects and in patients with different gastrointestinal disorders (Mózsik et al., 2013). These results are absolutely offered to exclude the privileged role of gastric acid secretion in the development of peptic ulcer disease in patients with gastric and duodenal ulcers;

5. To give a correct explanation for the together and simultaneously presence of ulcer with hyperacidity. It was clear at that time that the gastric acid secretion is a result of the very active metabolism; meanwhile, the development of ulcer was suggested as a consequence of impaired metabolism in the gastrointestinal mucosa. It was absolutely an unexplainable fact that both the gastric acid secretion (as an increased metabolic process) and the gastric ulcer (as a consequence of the impaired tissue metabolism) occur together and at the same time in the same organ;
6. In these years, we applied only anticholinergic drugs (together antacids) in the everyday medical treatment. If we suggest that these drugs are able to decrease the gastric acid secretion and if we apply the anticholinergic agent in the medical treatment, we can find a decrease in the metabolic process in the fundus of stomach. If we accept the presence of these decreased metabolic processes in the gastrointestinal tract, we can explain the healing process of ulcerated tissue and that really no hypoxemic presence exists in the ulcerated tissues around the gastric or duodenal ulcer in patients. If the last suggestion is true, than we contradict the generally suggested etiological theories published by the international experts;
7. We had no concrete information (knowledge) on the metabolism of gastrointestinal mucosa produced therapeutically (especially we had no information in this regard to humans).

We discussed very deeply our clinical pharmacological results obtained in patients with classical peptic ulcer disease. Our conclusion is that we do something (treatment) in the medical treatment; however, we have no concrete knowledge on the presence of the different biological events existing in the gastrointestinal tract.

We have to emphasize that we are in the second part of the 1960s–1970s. We had no knowledge of histamine-2 receptor antagonists, gastrin antagonist and, of course, proton pump inhibitors. The established clinical pharmacology helps us to select different compounds (from the medical practices), which were failures both clinically and pharmacologically (e.g., these agents are not absorbed from the gastrointestinal tract). These results offered clear pharmacological evidence to explain that the tertiary ammonium compounds absorb well from the

human GI tract, meanwhile the absorptions of the quaternary ammonium compounds failed. The aims of pharmacologists were the production of new quaternary ammonium compounds:

1. To produce new compounds with longer and stronger inhibitory actions on the gastric acid secretion in comparison to actions of tertiary ammonium compounds (and these were proved clearly in animal experiments);
2. The tertiary ammonium compounds are able to enter into the circulation of brain (going through the hemato-encephalic barrier), with the quaternary ammonium compounds not entering into thain circulation (through hemato-encephalic barrier).

The results of the established clinical pharmacology clearly indicated that the results of animal experiments can be accepted only with a significant criticism in the application of medical practice. It was also indicated clearly that the existence of clinical pharmacology is absolutely necessary in the pathways of new drug productions versus their clinical applications. The clinical pharmacology was established by us (Jávor et. al., 1965; Mózsik et al., 1965 a, b,;1967 a, b,;1969a,;Mózsik and Jávor, 1965 a, b,;1966 a, b, c,;1968 a, b; Mózsik, 1969a; Jávor, 1968) at Debrecen, Hungary (iuring tie period of 1—197 year.

Of course, there was a heated debate between the basic researchers and clinical pharmacologists, and the clinical pharmacologists prevailed over the basic researchers.

The classical pharmacology has been studied at our Department of Medicine of Universities (in Debrecen and Pécs, Hungary) up to now (2014) (Hunyady, 1997; Garamszegi et al., 1997; Mózsik et al., 1984d; Mózsik et al., 1985; 1986; 1997a; 1979c; 1981g; 1985; 1992e; Nagy et al., 1997; Patty et al., 1982; 1983; 1987; Tárnok et al., 1979; 1997).

Independently from the establishment of clinical pharmacology in patients with peptic ulcer, we wanted to know more and more on the nature of peptic ulcer disease. We tried to investigate and to know the most important possibilities of ulcer research:

1. The possibilities to approaches of neural effects in human patients with peptic ulcer were very complicated and their methodologies of clinicians were very limited. The increased activity of vagus nerve has been emphasized in the development of peptic ulcer disease. Clinically, our therapeutic possibility was only to apply the anticholinergic agents, which was the reason for starting with the clinical pharmacological evaluation of atropine treatment in patients with peptic ulcer;
2. The surgical intervention, as medical treatment, was frequently used in the 1970s. If the indication of surgery was based on the common consultations between the internists (later gastroenterologists) and surgeons (later gastrointestinal surgeons), then the “medical treatment” (generally for 4 weeks) was carried out as a primary therapeutic possibility, and this treatment was accepted as failed therapeutic process (the clinical pharmacology significantly decreased the number of patients with peptic ulcer disease who had to go over the surgical intervention).

The surgical tradition of Hungarian surgeons was based on the classical German surgical schools, and Billroth II surgical method was generally accepted by them. Only in the 1980s

surgical vagotomy appeared in the practice of Hungarian surgeons (Ihász, 1980). Consequently, we had no possibility to study and to follow these patients;

3. The possibility of the new therapeutic compounds was zero to clinicians;
4. There was little experimental ulcer research conducted in that time all over the world. Furthermore, experimental ulcer research was not effective in Hungary (these types of observations were done at First Department of Medicine, University of Szeged, Hungary, and were followed at Second Department of Medicine, University of Debrecen, Hungary, up to 1968 and thereafter at First Department of Medicine, University of Pécs, Hungary).

After a critical evaluation of our results obtained from our clinical pharmacology, we started in an absolutely unsure direction, namely the establishment of the biochemical approaches to gastrointestinal mucosa in the field of peptic ulcer research. (One of the authors, GyM, was the easy person.). This established biochemical research line was the first trend in peptic ulcer research in the World. We have to mention that the application of biochemistry in the ulcer research was a hard scientific challenge to us (because no similar attempts were existing in the World).

Of course, we tried to do some animal experiments (observations) to receive some practice in this field. Besides, we have to emphasize clearly that we wanted to study the different biochemical mechanisms in the gastrointestinal tract (obtained from the preparations at surgical intervention of patients with peptic ulcer).

Our principal aims were to obtain and to understand the reasons behind biochemical events in the gastrointestinal tract (during the ulcer development and at the time of gastric surgical interventions).

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