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Authors

Szabo, Sandor
Yoshida, Masashi
Filakovszky, Janos
et al.

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REVIEW ARTICLE

"Stress" is 80 Years Old: From Hans Selye Original Paper in 1936 to Recent Advances in GI Ulceration

Sandor Szabo*, Masashi Yoshida, Janos Filakovszky and Gyorgy Juhasz

Departments of Pathology and Pharmacology, School of Medicine, University of California, Irvine, CA, USA; Department of Surgery, International University of Health and Welfare Hospital, Tochigi, Japan; Selye Janos University, Komarno, Slovakia

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Abstract: The first scientific publication on 'general adaption syndrome', or as we know today 'biologic stress' has been published in Nature in 1936 by the 29-year old Hans Selye. His results in that short publication that contained no references or illustrations, were based on experiments in rats that were exposed to severe insults/stressors, but his idea about a 'nonspecific bodily response' originated from his observations of sick patients whom he had seen as a medical student and young clinician. Autopsy of stressed rats revealed three major, grossly visible changes: hyperemia and enlargement of the adrenals, atrophy of the thymus and lymph nodes as well as hemorrhagic gastric erosions/ulcers (the "stress triad"). Based on this and additional observations, he concluded that the key master organ in stress reactions is the adrenal cortex (although he also accepted the limited and short lasting effect of catecholamines released from the adrenal medulla) which stimulated by an increased secretion of ACTH, secreted by the anterior pituitary gland. He thus identified the first molecular mediators of the stress reaction, *i.e.*, steroids released from the adrenal cortex that we call today glucocorticoids, based on his classification and naming of steroids. At the end of a very productive life in experimental medicine, Selye recognized that under both unpleasant and demanding stressors as well as positive, rewarding stimuli adrenal cortex releases the same glucocorticoids and only certain brain structures may distinguish the stimuli under distress and eustress - terms he introduced in 1974, that also contained his last definition of stress: the nonspecific response of the body on any demand on it. After brief description of the history of stress research, the rest of this review is focused on one element of stress triad, *i.e.*, gastroduodenal ulceration, especially its pathogenesis, prevention and treatment. Following a short description of acute gastroprotection, discovered by one of Selye's students, we discuss new molecular mediators of gastroduodenal ulceration like dopamine and new drugs that either only heal (very potently, on molar basis) or prevent and heal ulcers like sucralfate derivatives and the relatively new peptide BPC-157. We conclude that despite the extensive and multidisciplinary research on stress during the last 80 years, a lot of basic and clinical research is needed to better understand the manifestations, central and peripheral molecular regulators of stress response, especially the modes of prevention/management of distress or its transformation into eustress and the treatment of stress-related diseases.

Keywords: Stress, history, distress, eustress, stress triad, gastric and duodenal ulcers, cysteamine, propionitrile, dopamine, MPTP, Parkinson's disease, angiogenic growth factors, sucralfate, BPC-157.

1. INTRODUCTION

The recently published best-seller book entitled "The Invisible History of the Human Race: How DNA and History Shape our Identities and our Futures" [1] concludes with an interesting statement: "It is also the case that the environment modulates genes, but which elements of the environment exactly? How well you slept as a child? (…) The absence or presence of certain stressors matters too. Did you grow up in a war zone? Did your family live in poverty?" What an interesting sign of progress in science history: starting the "stress" field with a short article, based on animal experiments, published in one of the best scientific journals of the world [2], despite initial rejection and criticism, the field of stress research reached virtually all fields and branches of biomedical sciences. Hans Selye complained many times that initially he had to fight to get his stress response, that was first called "general adaption syndrome" (GAS) [3], accepted in the 1940s and 1950s, but later on, *e.g.*, in the 1970s and 1980s he had to argue not to use the word "stress" uncritically and loosely [4].

Another good illustration of how far the basic research of stress progressed over about seven decades is the description of societal stress, in another recent bestseller book: "Timothy J. Bowers, a sixty-two-year-old man in Ohio, struggled to find a good, stable job after the drug wholesale company for which he made deliveries closed. After a fruitless three-year search, he came up with a plan to get by until he was old enough to receive Social Security [benefits]. After handing over his apartment keys to his landlady, he told her that he probably would not be back. He then walked a few blocks to a bank, went inside, handed a teller a note, received $80, and then turned the money over to the bank's security guard and waited for the police to arrive and arrest him. At his trial, Bowers explained to the judge that with only minimum-wage jobs available to him, going to jail for three years would 'suit me fine' since, upon his release from prison, he would be sixty-six years old and thus old enough to receive his full Social Security benefits. In a New York Times article that satirically describes Bowers as 'an honest-to-goodness visionary' in the realm of retirement planning, Bowers's attorney, Jeremy W. Dodgion, described Bowers's actions as a sign of the times, stating, 'At his age, it was harder and harder to find a job with benefits, [so] he finally said, to hell with it.' After three years of barely getting by, of going without health care and sick leave, of worrying about where his next dollar would come from and with his future prospects bleak, Mr. Bowers decided that jail would be preferable to his life of insecurity. (…) For what Mr. Bowers sought when he robbed the bank so he could go to jail wasn't simply [free] room and board. What he sought was emotional relief from his arduous three-year struggle [*i.e.*, distress] to make ends meet" [5]. These are the dramatic first sentences of the

*Address correspondence to this author at the Department of Pathology, University of California-Irvine Sch. of Med., Irvine, CA 92625; Fax: 949-644-7325; E-mail: sszabo@uci.edu

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recently published book of the Stanford University sociologist Marianne Cooper [5, 6].

After these powerful illustrations of how far stress research implications reached 80 years after its inception [2], this review article is focused on the historic perspectives of biologic stress, the importance of morphologic 'triad of stress', of which gastroduodenal ulceration will be further analyzed for its pathogenesis, especially the new molecular mediators like dopamine, mostly based on contributions from our laboratories. We will finish by reviewing the possibilities of ulcer prevention vs. treatment.

2. HISTORIC PERSPECTIVES

The concept of stress or stress response/reaction or GAS, as it was initially called [2], was the first major discovery of Hans Selye. The concept was proven and refined in animal models (mostly rats), but as he described in many of his books [3, 7-9], he got the idea after observing many of his sick patients as a medical student and young physician at the German university in Prague. Namely, he saw that despite being sick because of certain organ malfunction (*e.g.*, cardiac, pulmonary or gastrointestinal diseases), there was a 'common look' in all these patients, *i.e.*, just being ill, showing mild or severe lethargy, sometime even depression… As we know today, some of these signs and symptoms may be ascribed to adrenal insufficiency, the master organ of the stress response. Actually, these nonspecific symptoms (*e.g.*, mild or severe lethargy) were seen in early HIV patients in the 1990s and when autopsy revealed adrenal atrophy, subsequent patients were given cortisol or cortisone that not only improved the appearance and mood of these sick people, but also prolonged their life by 6 or more months [10].

After he left Prague for a short research fellowship in the early 1930s at the Johns Hopkins University in Baltimore, USA, he continued his research related to find explanations for the common manifestation of diseases in the Anatomy Department of McGill University, in Montreal, the oldest and best institution of higher education in Canada. There, in his modest laboratory, initially he was looking for new ovarian hormones (steroids), stimulating female rats with various chemicals. He noticed that instead of ovarian changes, the adrenal glands of animals were enlarged, often associated with atrophy of the thymus and spleen. He then had the creative idea that maybe these changes are nothing to do with certain stimuli and they may represent some nonspecific response of the body. Based on this hunch, he injected rats subcutaneously with small doses of toxic formalin or exposed the animals to extreme cold on immobilized them of restraint boards for 4-18 hr. Interestingly, but not so surprisingly, at autopsy all these rats had not only enlarged adrenals, atrophic thymus, spleen and lymph nodes, but they also showed hemorrhagic gastric erosions (or ulcers). Needless to say these rats, at the end of experiments, 'looked sick', lethargic – reminding Selye of his observation of sick patients in Prague. Hence, the concept of nonspecific response was born, with manifestation of morphologic triad, *i.e.*, adrenal hypertrophy, atrophy of thymo-lymphatic system and gastric ulcers. He described the whole phenomenon as 'nonspecific response' or GAS in his first, short scientific article (which didn't need to have a single reference since the concept was so unique and original) and published in one the best scientific journals or the world, *i.e.*, in Nature in 1936 [2].

Although Selye discovered the "biologic stress response," initially he did not use the word "stress". Namely, his historic article 80 years ago [2] had the title: "A syndrome produced by diverse nocuous agents", and the word "stress" was not used until his first comprehensive monograph [3] on the subject published in 1950 in Montreal had the short title "Stress" (Fig. **1**). This was followed by a series of "Annual Reports of Stress" published during the subsequent five years by the same publisher. Selye's first definition of stress was "the nonspecific neuroendocrine response of the body" [3, 7, 8]. Later on he dropped the "neuroendocrine" because he

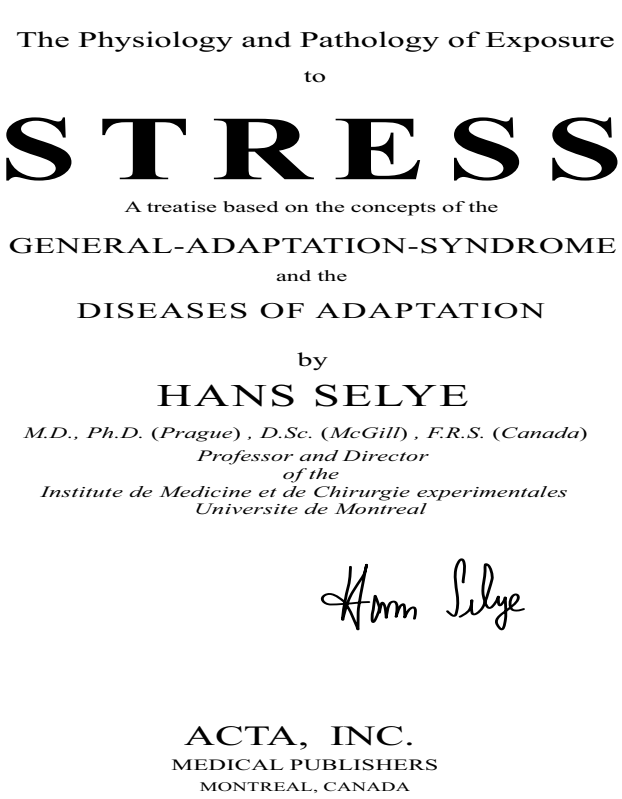
The Physiology and Pathology of Exposure
to
STRESS
A treatise based on the concepts of the
GENERAL-ADAPTATION-SYNDROME
and the
DISEASES OF ADAPTATION
by
HANS SELYE
M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada)
Professor and Director
of the
Institute de Medicine et de Chirurgie experimentales
Universite de Montreal
Hans Selye
ACTA, INC.
MEDICAL PUBLISHERS
MONTREAL, CANADA

Fig. (1). Cover page to the first monograph by Hans Selye on stress published in 1950.

realized that in addition to involvement of the neuroendocrine system, almost every other organ system (*e.g.*, especially the cardiovascular, pulmonary and renal systems) is also affected in one or several stages of stress response, *i.e.*, in the alarm reactions, stage of resistance and/or stage of exhaustion [11, 12]. Yet, he never gave up the emphasis of nonspecificity as the main characteristics of stressors, *i.e.*, various agents that cause stress. Namely, we know from his books [3, 7, 8, 11, 12] and personal communications with him [4] that he was greatly concerned by criticism in the late 1940s and early 1950s that he named both the cause and effect as "stress". Hence, being very prone to create new names and definitions, he started to use the word "stressor" as the factor/agent that triggers the "stress" response. He went out of his way to emphasize that the stressor may be physical (*e.g.*, cold, heat), chemical (*e.g.*, formalin, ether), or psychologic in nature.

2.1. The Importance of Non-Specificity

Selye's favorite example of specific vs. nonspecific, *i.e.*, stressor effects of insulin (Fig. **2**). He used a variant of this figure in almost all his lectures on stress, emphasizing that insulin injection decreases blood glucose levels (specific effect of this hormone), yet in large doses, especially after repeated injections in experimental animals, it causes stress reaction, *i.e.*, elevates the secretion of catecholamines and corticoids, with consequent morphologic changes of "triad of stress" (Fig. **3**) [2, 3, 7, 8, 11, 12]. Yet, at the end of his life, he complained that people used the term "stress" almost indiscriminately, *i.e.* "it was hard to get acceptance in the 1940s – now it's almost a household term" [4]. Namely, he used to say that nobody should call an effect "stress response" until the same effect is reproduced by several stressors different in nature, *e.g.*, physical and chemical stressors. He was concerned that reviewers/editors of reputable scientific journals would allow the label of "cold stress" or "ether stress" without using any other stressors to ascertain whether the changes monitored reflect a specific

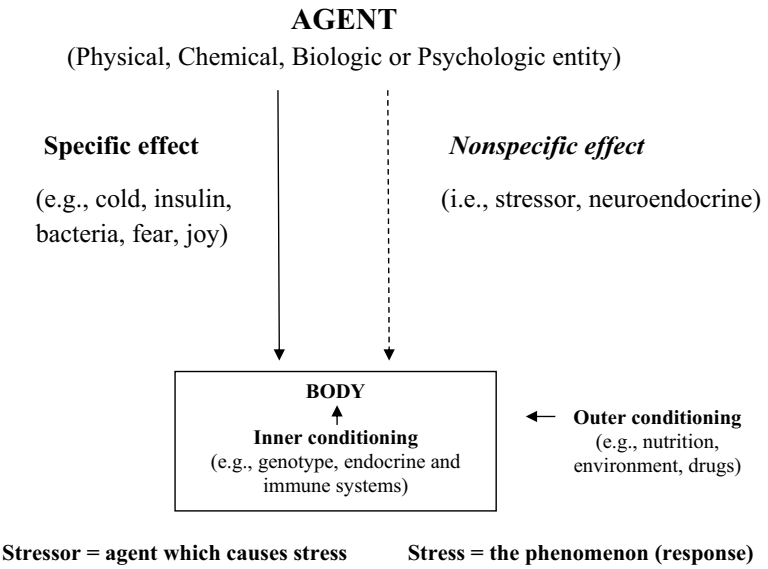

Fig. (2). Illustration of the specific and nonspecific *i.e.*, stressor effect of various agents (Modified from Szabo, 1998).

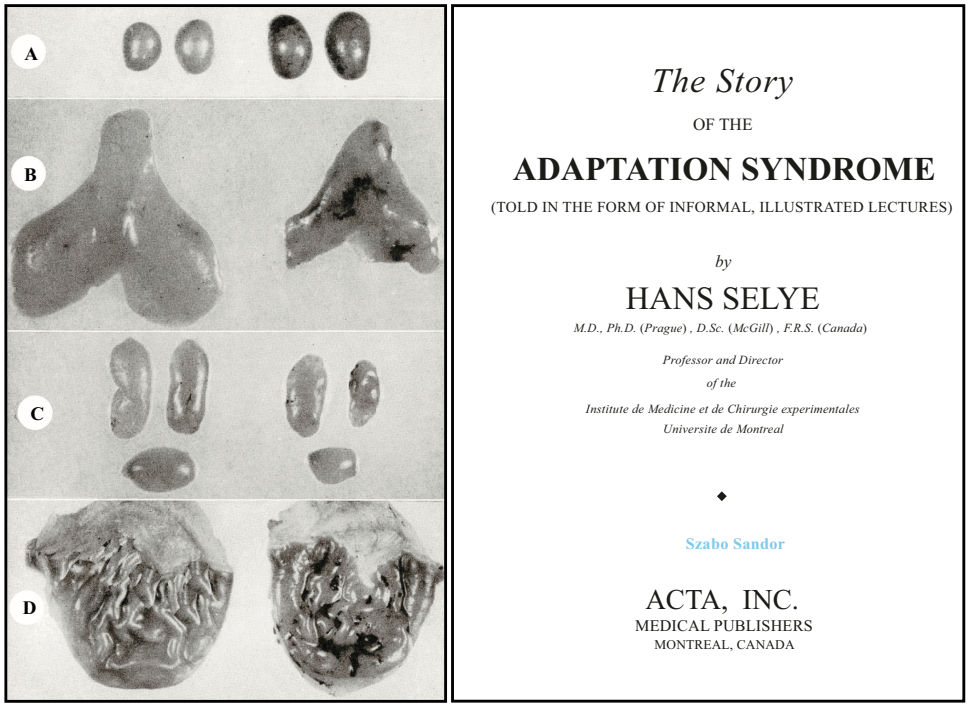

Fig. (3). The typical triad of the alarm reaction. **A.** adrenals, **B.** thymus, **C.** iliac lymph nodes, **D.** gastric mucosa of a normal rat (left) and one which was exposed to the frustrating mental stress of being immobilized on a metallic board for 24 hours. Note the marked enlargement with lipid discharge and hyperemia of the adrenals (which consequently became reddish-brown), the intense atrophy of the thymus and lymph nodes and the numerous blood-covered gastric erosions ulcers in the stressed rat (right) (Modified from Selye 1952).

response to a stimulus or a nonspecific response also induced by various stressors.

Although Selye never wavered from emphasizing that the stress is nonspecific, but after four decades Selye recognized that not all stress reactions are equal (despite the stereotypical neuroendocrine effects), due to difference in the subject's perception and emotional reaction. As he admitted [4], the clinical and social investigations of Lenard Levi in Sweden [13] played a major role in Selye's shift of thinking. Namely, until the end of his life, Selye remained a basic science researcher who never moved beyond the use of animal models of stress-related disorders. Yet, as avid and compulsive reader of medical literature, he was pleased to see that his initial, often criticized basic investigations of the 1930s-1950s were expended by others to clinical fields, and later to sociology and psychology. It was Levi who first distinguished between "positive" and "negative" stress [13], *i.e.*, our brain cortex may recognize the difference if ACTH and corticoids were released under the influence of arguments with our spouse, or because of the pleasure of receiving an Olympic medal or a major reward at one's workplace.

The creative Selye, always ready to create new names and concepts, introduced the terms "distress" and "eustress" (à la euphoria) in the early 1970s, to distinguish if the stress response was initiated

by negative, unpleasant stressors, or positive emotions [14]. He was so convinced that this was a major distinction and discovery relevant not only to the relatively small scientific/research community, but to the general public, that he published this new distinction in a book "Stress without distress" [14]. In the subsequent autobiographic "Stress of my life" [9] he started to emphasize that "stress is not what happens to you, but how you react to it" [12, 14]. Although the distinction between distress and eustress is about 40 years old, the molecular mediators of these two stressors are still lacking; though it's emerging that in chronic distress the expression of brain-derived neurotrophic factor (BDNF) and the activity of anti-apoptotic enzyme Bcl-2 are decreased leading to oxidative tissue damage, especially in the hippocampus [15,16].

2.2. Classification and Naming of Steroids, *e.g.*, Glucocorticoids

Hans Selye knew form his very early experiments with stressed animals that in hypophysectomized rats one cannot see the morphologic triad of stress. He soon connected this to the lack of ACTH which stimulates the secretion of adrenocortical glucocorticoids. Actually, he has been interested in steroids much before and after the discovery of GAS and in the early 1940s he published seminal papers on the classification and naming of steroids (Table **1**) [17-19]. He very cleverly named these hormones by the source of their origins, *e.g.*, corticoids (originating in the adrenal cortex), testoids (originating from the testes), folliculoids and luteoids (produced by the follicles and corpus luteum of the ovary, respectively). It's easy to recognize that these are the present-day corticoids, androgens, estrogens and progestins. Selye, who was also a chemist (his PhD, obtained after the MD degree in Prague, was in chemistry), also based this classification on the chemical structure of steroids, *e.g.*, containing 21, 19 or 18 carbons, respectively [17-19]. This chemical and structural approach to steroids in the 1930s and 1940s actually may be interpreted as one of the first molecular, mechanistic definition of stress reaction.

He also acknowledged the contributions of catecholamines, especially in the alarm reaction phase of GAS, since he was familiar with Cannon's "fight or flight" syndrome that was associated with the rapid and massive release of epinephrine (adrenaline) and norepinephrine (noradrenaline), mostly from the adrenal medulla [20]. Glucocorticoids are, nevertheless, responsible for most of the morphologic manifestations of distress, especially, in the "stages of resistance and exhaustion" [3, 11, 12]. As an illustration, in a bisected adrenal gland contains the names of these scientists in the appropriate parts of the gland (Fig. **4**).

Table 1. Classification and naming of steroids by Hans Selye (*Science, 1941*; *Nature, 1943; Endocrinology, 1942; 1944).*

The Selye- and the current classification of steroids	
• ***Selye***	***Modern***
– Corticoids =	Corticoids ("cortico-steroids")
– Testoids =	Androgens
– Folliculoids =	Estrogens
– Luteoids =	Progestins

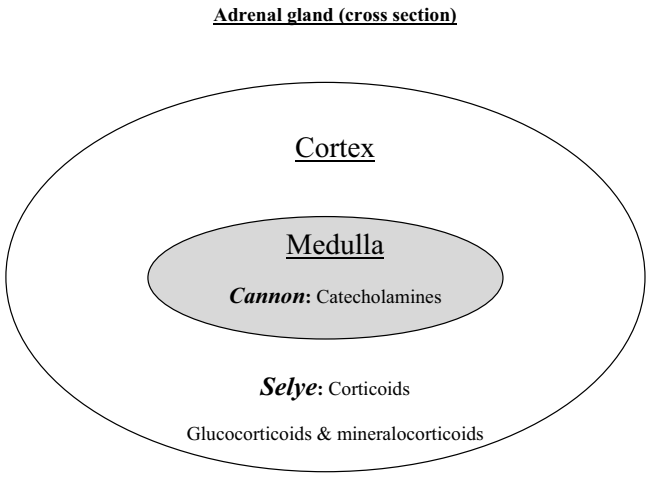

Fig. (4). The organ-specific contributions of Hans Selye & Walter Cannon in the stress reaction of the adrenal gland (Modified from Szabo 1998).

We also must emphasize another major contribution of Selye, *i.e.*, the discovery of anti-inflammatory action of glucocorticoids. Namely, glucocorticoids and mineralocorticoids (also named by Selye) regulate not only carbohydrate and mineral/electrolyte metabolism, respectively, but they also exert anti- or pro-inflammatory effects [21-31]. These pioneering findings were published in the most prestigious research and clinical journals of all times in early and mid-1940s. Especially noteworthy is his publication on "Relation of the adrenal cortex to arthritis" in Lancet 1946 [29]. Yet, the 1950 Nobel Prize in Physiology or Medicine was awarded to the clinician Dr. Philip Hench (and the two chemists who isolated and identified the structure of glucocorticoids) who demonstrated the "next obvious step", *i.e.*, that cortisone and ACTH exert clinically profound anti-inflammatory effect in patients with rheumatoid arthritis [32].

3. THE 'STRESS TRIAD' – FOCUS ON GASTRODUODENAL ULCERS

Although the morphologic triad of stress, as initially described by Selye [2, 3] also includes adrenal enlargement, thymo-lymphatic atrophy, the remaining part of this review article will be focused on gastrointestinal (GI) ulceration, especially gastroduodenal ulcers. The acute "ulcers", seen mostly in the stomach of stressed animals, are actually superficial hemorrhagic erosions, *i.e.*, they don't penetrate the *muscularis mucosae* of the stomach or duodenum [32, 33]. These lesions, since they involve only necrosis of the mucosal epithelial and connective tissue cells that replicate easily, heal rapidly, while deep ulcers that also involve necrosis of smooth muscle (*e.g.*, *muscularis propria*), heal only after the angiogenesis-dependent granulation tissue has been covered by epithelial restitution and replication [32, 34].

The cause of acute "stress" ulcers historically has been ascribed to the massive release of glucocorticoids and catecholamines during the alarm reaction, especially, since these vasoactive amines cause constriction of blood vessels that create an ischemic condition which predisposes the gastroduodenal mucosa to the damaging action of gastric acid [3, 12]. Indeed, this pathogenesis, based on initial animal experiments, has been widely confirmed by clinical observations, like gastroduodenal ulcers in people with extensive burns [35, 36] and in severely ill patients in intensive care units [37, 38]. Surgeons know this best: although the incidences of gastric ulcers have declined during the last about 20 years, but the sever clinical complications of perforated and penetrated duodenal ulcers

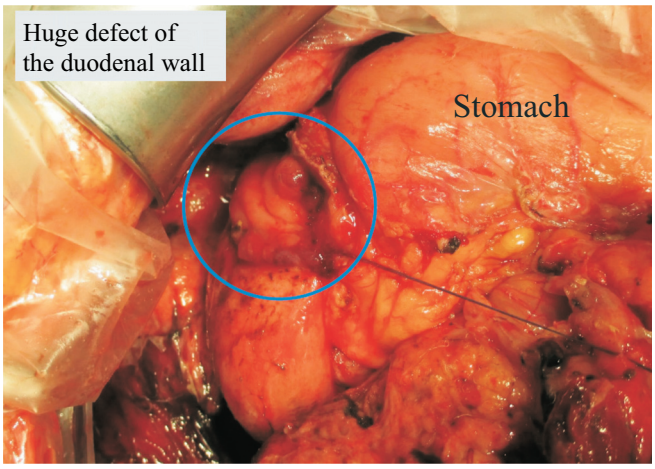

Fig. (5). A surgeon's view of a large, perforated duodenal ulcer in a patient (Courtesy of Prof. Yoshida, 2016).

(Fig. **5**) remained essentially the same (39]. Furthermore, we also know from numerous clinical observations and case reports that about 10-30 % of people ingesting large doses of anti-inflammatory glucocorticoids or Non-Steroidal Anti-Inflammatory Drugs (NSAID) come down with GI ulcers [40 - 42].

New experimental studies suggest that the deleterious effect of glucocorticoids may be biphasic, *i.e.*, at low, physiologic levels they may exert gastroprotection. The first results came from adrenalectomized rats that didn't respond to the usual gastroprotective doses of prostaglandins (PG) and to non-PG gastroprotective drugs [43, 44]. Furthermore, when these adrenalectomized animals were maintained on daily physiologic doses of corticosterone (the naturally occurring glucocorticoid in rodents), but not that of desoxycorticosterone (DOC, the natural mineralocorticoid in rats), the animals showed the same gastroprotective response to PG against ethanol or aspirin, as normal control rats given PG [43]. These early results have been greatly extended by recent studies of Filaretova and coworkers who definitely demonstrated a biphasic, gastroprotective effect of natural glucocorticoids [45, 46], but also confirming that large doses of glucocorticoids produce gastric ulcers.

The concept of "gastric cytoprotection" or gastroprotection was actually introduced by Andre Robert, a former PhD student of Hans Selye [47, 48]. These creative experiments demonstrated that pretreatment of rats with small, not antisecretory doses of PG prevented the acute hemorrhagic gastric erosions caused by concentrated ethanol, acid or base or boiling water [47] . Subsequently it was shown that cimetidine and probanthine, in doses that do not inhibit gastric acid secretion, also prevented these chemically induced gastric lesions that were much more severe and extensive than the small acute "stress ulcers" [49]. Based on these new findings we postulated some common endogenous molecules that may mediate the protective effect PG and non-PG drugs. Indeed, we found, as described above, that endogenous glucocorticoids are essential for this acute gastroprotection [43, 44]. We also found the involvement of another common endogenous protective molecule, *i.e.*, reduced glutathione (GSH), since we demonstrated that ethanol depletes this endogenous antioxidant in the gastric mucosa before the appearance of gastric erosions in ethanol-treated rats [50]. Furthermore, pretreatment of rats with sulfhydryl (SH) containing chemicals (*e.g.*, cysteine, N-acetyl cysteine or Mucomyst, methionine) also exerted gastroprotection, similar to that seen after the administration of small doses of PG [44, 50]. To reinforce the role of endogenous SH antioxidants in gastroprotection, we were pleased to learn that the SH alkylators N-ethylmaleimide (NEM) or iodoacetamide counteracted the PG-induced and other forms of gastroprotection [50]. As it turned out with the subsequent studies of Wallace *et al*., some of these endogenous SH-containing chemicals are precursors of hydrogen sulfide (H_2S) that also protects the gastric mucosa, probably via maintaining mucosal vascular integrity and blood flow [51, 52]. Thus, these post-Selye studies demonstrated at least three new protective chemicals and mechanisms in preventing stress-like gastric erosions, *i.e.*, glucorticoids, SH-containing antioxidants and the gaseous H_2S.

The relevance of morphologic stress triad, especially the associated gastric erosions/ulcers is also confirmed by another important observation of Selye's former students Andre Robert. Namely, he demonstrated a similar cross resistance that Selye published after finding that exposure of rats to a mild, early stress prevented the morphologic triad induced by subsequent sever stress [53]. Robert, most likely being familiar with these previous stress experiments, gave rats small doses of alcohol (*e.g.*, 1 ml of 20% ethanol) 15-30 min before gavage of 1 ml of 96% ethanol and found that the hemorrhagic gastric erosions were prevented [54]. This "adaptive gastric cytoprotection" as he called it was counteracted by indomethacin which blocks the PG generating cyclo-oxygenase [54] or the SH alkylating NEM, indicating that both endogenous PG and SH compounds are involved in adaptive gastroprotection [52]. Furthermore, subsequent studies in various laboratories during the last two decades demonstrated that virtually all forms of gastroprotection have been counteracted by NEM - much more frequently than indomethacin was able to achieve that [55-59].

We cannot finish the review of triad of stress, initially discovered in animal models, without commenting on the human relevance of 'stress ulcers'. This topic is especially important now, after the discovery of the role of H. pylori in the pathogenesis of human gastritis and possibly, in 'peptic ulcers' [60, 61]. Namely, after the recognition of this bacterium in gastroduodenal diseases, a lot of investigators and clinicians claimed that virtually all human gastroduodenal ulcers are caused by infection and stress plays virtually no role [61, 62]. Yet, these authors seem not to be aware of the very relevant publications from early 1940s, in part authored by Hans Selye [63] who called attention to several case reports on the overnight increase in perforated gastroduodenal ulcers in seemingly healthy, but distressed British population after rocket bombing of London during World War II [64-66] . These clinical reports were based on objective data, mostly based on overnight post-bombing admissions to London hospitals. Obviously, nobody would claim that these patients got H. pylori infection overnight that rapidly caused perforating gastroduodenal ulcers… Rather, like in experimental animals, the stressors (*e.g.*, fear of dying, or being injured, food deprivation bordering on fasting, cold) produced sever gastroduodenal ulcers. Thus, nowadays, the most objective and not-opinioned clinicians and investigators, who are aware of the raising proportions of H. pylori-negative ulcers, agree that the major cause of human gastroduodenal ulcers are NSAID and stress [67-70]. This is also supported by 15-years of H. pylori eradication programs in Japan [39] that resulted in gradual decrease of gastritis and gastric ulcers, but not in the prevalence of duodenal ulcer-related mortality (Fig. **5**).

These data do not, of course, exclude the role of this bacterium in the pathogenesis of human ulcers. Our animal model and *in vitro* results suggest that H. pylori may not cause gastric or duodenal ulcers (as other investigators could not induce ulcers by this bacterium in experimental animals – thus, never satisfying the Koch postulate) [62], but it may delay the healing of ulcers induced by exogenous chemicals or stress [70]. Namely, lysates of H. pylori decreased the bioavailability of angiogenic growth factors like bFGF or PDGF that are crucial for ulcer healing, most likely because of the proteolytic activity of these lysates that accelerate the degradation of ulcer healing peptide growth factors [71-73]. Thus, H. pylori may not cause ulcers, but it seems to delay the healing of gastroduodenal lesions induced by stress or drugs [34, 70, 74]. It is

then not surprising that – like with any other infectious agent – after treatment with appropriate antibiotics the bacteria are eradicated, ulcers, like any other external wounds, heal spontaneously.

Hence, stress-induced gastroduodenal ulcers, unfortunately, are also 'alive and well' in the general population and very often in intensive care unit patients [75-77]. Namely, several recent epidemiologic studies documented increased incidence of gastroduodenal ulcers in societies undergoing rapid, mostly stressful change (*e.g.*, in South Africa, Hong Kong, China) [78-80]. The problem of so-called stress ulcers in severely ill patients in intensive care units also remains a major medical challenge, especially, since neither antacids/antisecretory drugs nor sucralfate-like drugs are fully effective in preventing these ulcers – or the treatment with antisecretory creates more severe side effects like aspiration-induced pneumonias [81, 82]. Thus, unfortunately, stress-induced gastroduodenal ulcers almost represent as much as scientific problems and public health concerns as 70-80 years ago.

4. PATHOGENESIS OF GASTRODUODENAL ULCERATION – FOCUS ON DOPAMINE

The sequence of mechanistic events (molecular and cellular changes), *i.e.*, pathogenesis can be best studied in animal models of the disease. As Selye used to say [4], we need good animal models, since in patients we may investigate only what makes the disease active and how we may accelerate the healing process. Until the 1970s, unfortunately we only knew about gastric acid and pepsin being etiologic factors in gastroduodenal ulceration, despite the fact that only about 50% of duodenal ulcer patients have higher than normal gastric secretion [83]. And since Duodenal Ulcers (DU) are 2-4 times more frequent than gastric ulcers, in the subsequent review of pathogenesis, we will focus mostly on duodenal ulceration – but we point out the excellent and very comprehensive article of Prof. Brozowski in this issue of Curr. Pharm. Design that reviews most of endogenous molecules, discovered during the last about three decades, to play a role in gastric ulceration and gastroprotection [84].

Although DU are more frequent in people, it has been extremely difficult to reproduce DU in laboratory animals since large doses of glucocorticoids, aspirin or other NSAID induce only gastric erosion or ulcers in rodents (*i.e.*, rats, mice). Fortunately, we found by serendipity during toxicology studies in Selye's institute that certain chemicals selectively induce DU. The first rapidly developing DU was found to be induced by acetanilide. However, the incidence of acetanilide-caused DU in the rat was low, and the model was not studied further. Subsequently, we found that propionitrile and cysteamine selectively induce DU in rats [85, 86]. The lesions occurred 3-5 mm from the pylorus, mostly on the antimesenteric or anterior wall of the duodenum, and developed within 24-48 hr of administration after cysteamine. By several structural and functional criteria these experimental ulcers closely resembled human DU [87]. Gastric ulcers rarely occurred and the DU showed a tendency to perforate into the peritoneal cavity or penetrate into the liver or pancreas, thus closely resembling the anatomic disposition of human DU. We also demonstrated a structure-activity relationship between alkyl and aryl chemicals that allowed us to predict the duodenal ulcerogenic property of other chemicals and to demonstrate for the first time that DU induction is not a surprising side-effect but a predictable action of certain chemicals which initiate a series of biochemical and cellular changes both in the peripheral organs (*e.g.*, duodenum, stomach) and brain [88-93]. Among the prerequisites for DU induction is a 2-carbon backbone bearing electronegative radicals and this recognition allowed us to identify other endogenous molecules (since cysteamine is also a natural product, being part coenzyme A) that may play a role in the pathogenesis of DU.

Studies with *exogenous* duodenal ulcerogens allowed us to develop new animal models and look for *endogenous* mediators and modulators of duodenal ulceration. We recognized that structural

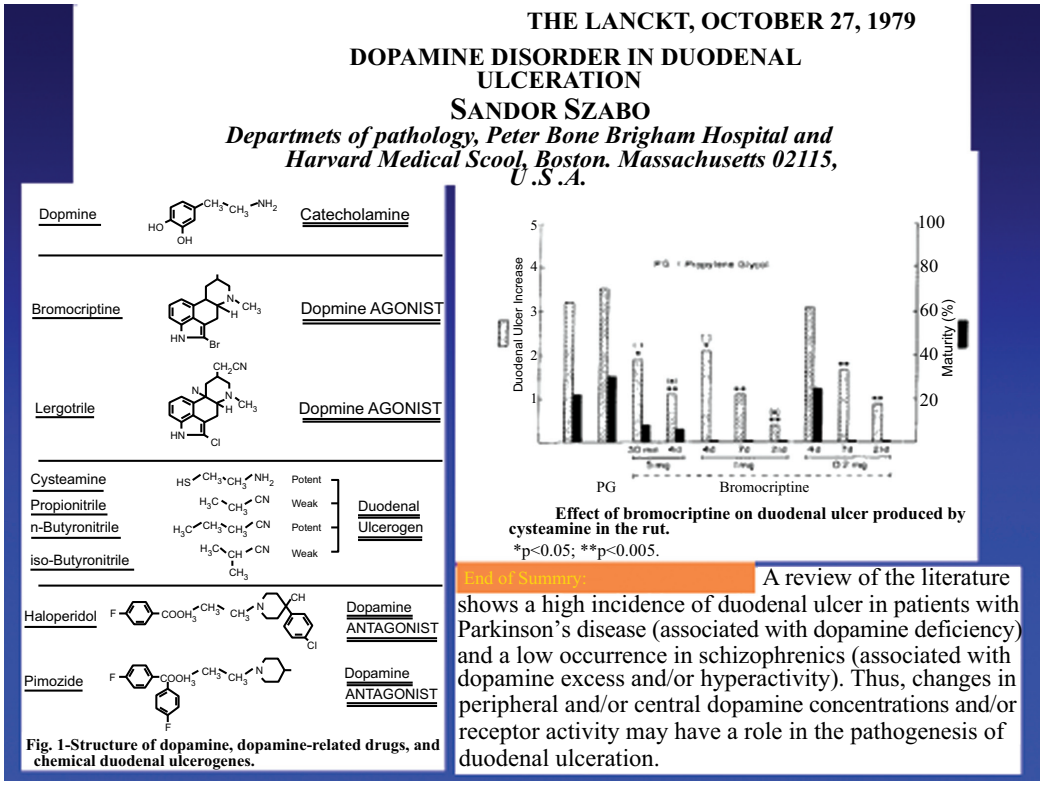

Fig. (6). The structural similarities between duodenal ulcerogenic chemicals and dopamine-related drugs. The dose- and time-dependent antiulcerogenic effects of bromocriptine in the cysteamine-induced duodenal ulcer model in rats. Clinical relevance: susceptibility in Parkinson's disease to gastroduodenal ulceration (adapted from Szabo, 1979).

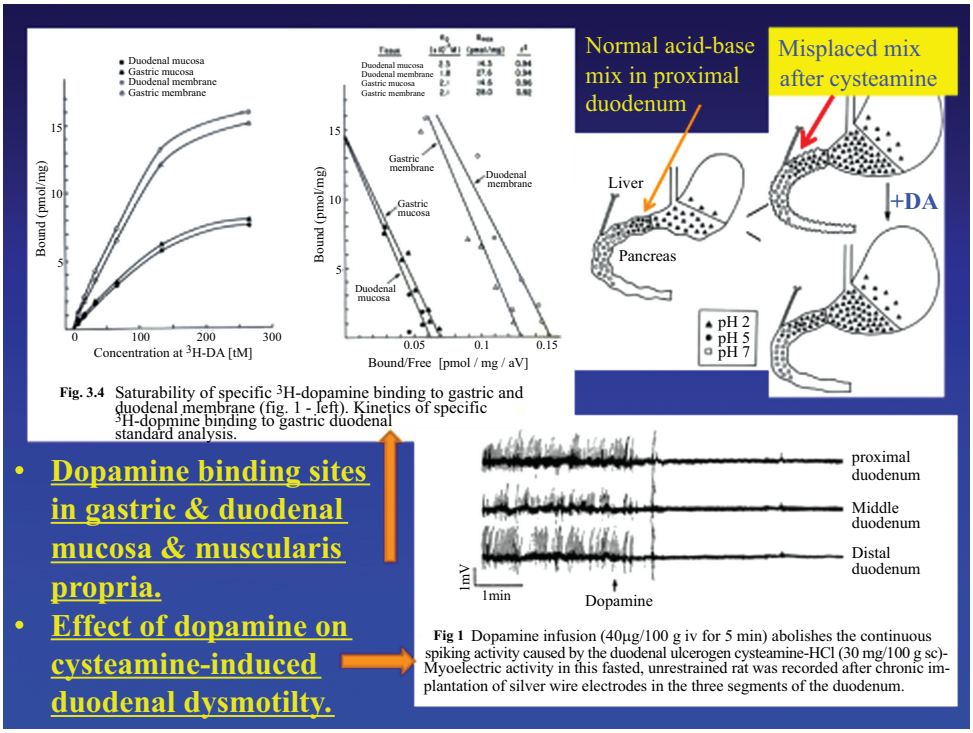

Fig. 3.4 Saturability of specific ^{3}H-dopamine binding to gastric and duodenal membrane (fig. 1 - left). Kinetics of specific ^{3}H-dopmine binding to gastric duodenal standard analysis.

Fig 1 Dopamine infusion (40µg/100 g iv for 5 min) abolishes the continuous spiking activity caused by the duodenal ulcerogen cysteamine-HCl (30 mg/100 g sc)-Myoelectric activity in this fasted, unrestrained rat was recorded after chronic implantation of silver wire electrodes in the three segments of the duodenum.

Fig. (7). Dopamine binding in the mucosa and muscularis propria of the stomach and duodenum (please note the twice more binding sites in the muscle than in the mucosa). The functional relevance: Duodenal dysmotility induced by cysteamine is counteraction by dopamine (adapted from Szabo *et al*., 1982; Gallagher & Szabo, 1984; Pihan - Szabo, 1985).

similarities exist between cysteamine and endogenous ethylamines such as histamine, serotonin, dopamine, acetylcholine and GABA. Since the role of histamine and acetylcholine in gastric secretion and gastroduodenal pathophysiology is widely known, we focused on investigating the possible role of dopamine (Fig. **6**) in duodenal ulceration while acknowledging that serotonin and GABA may also be involved. We found that dopamine agonists or precursors prevented, while the dopamine antagonist and catecholamine depletors aggravated the cysteamine-induced DU duodenal ulceration (Fig. **6**) [92-94]. These findings strongly suggest that dopamine, centrally and peripherally, may be involved in the pathogenesis of duodenal ulceration. Indeed, in rats cysteamine and propionitrile time dependently decreased the concentration of dopamine in certain brain regions as well as in gastric and duodenal mucosa [95-97]. Furthermore, for the first time, we also identified dopamine binding sites in gastroduodenal mucosa and *muscularis propria* (Fig. **7**) [98].

The hypothesis that dopamine may be novel endogenous modulator of DU is further supported by our prediction that the dopaminergic neurotoxin MPTP, which induces Parkinson's disease in man and experimental animals, would produce DU in rats. Indeed, we published that multiple injections of MPTP in rats induced severe DU, like those seen after cysteamine administration [92, 99]. The MPTP-induced DU was prevented by the MAO-B antagonist l-diphenyl that elevates endogenous dopamine levels [99].

We emphasize that all the compounds mentioned above, including cysteamine and MPTP produce similar ulcers on the anterior and posterior wall of the proximal duodenum. The gross and light microscopy of these experimental DUs is rather uniform, and as in humans, but the pathogenesis might be slightly different, as in patients where only about half of people with DU have increased gastric acidity [83]. Dose- and time-response studies with dopamine agonists and antagonists using the cysteamine and propionitrile DU models in the rat demonstrated that the chemically induced DU were prevented by the dopamine agonists bromocriptine, lergotrile (Fig. **6**) [93] and reduced by apomorphine or L-DOPA (*i.e.*, dopamine precursor) [90]. Aggravation of cysteamine-induced DU was seen especially after (-)-butaclamol, (-)-sulpiride, haloperidol and, less effectively, after other dopaminergic antagonists. The duodenal antiulcerogenic action of dopamine agonists was more prominent after chronic administration than after a single dose, whereas the opposite was found concerning the proulcerogenic effect of dopamine antagonists [93].

In the chronic gastric fistula rat, both the antiulcerogens bromocriptine or lergotrile and the proulcerogens haloperidol, pimozide or (-)-N-(2-chlorethyl)-norapomorphine decreased the cysteamine- or propionitrile-induced gastric secretion [96, 100]. No correlation was apparent between the influence of these drugs on duodenal ulcer development and gastric and duodenal (pancreatic/biliary) secretions. In the chronic duodenal fistula rat, decreased acid content was measured in the proximal duodenum after haloperidol, and diminished duodenal pepsin exposure was recorded after bromocriptine [101]. Thus, the effect of dopamine-related drugs on DU developments seems to be independent of their effects on gastric secretion, but it may be related to the motility stabilization effect of dopamine on cysteamine-induced duodenal fibrillation/dysmotility that interferes with the retrograde flow of pancreatic bicarbonate and hepatic bile flow to the proximal duodenum where DU develops [101, 102] (Fig. **7**). Nevertheless, the site and role of central and peripheral dopamine receptors that influence DU development remain to be identified, but their elucidation may prove to be an important element in the pathogenesis and treatment of DU.

These results, obtained in animal models strongly implicate dopamine in the pathogenesis of duodenal ulceration (Fig. **8**) and this is further reinforced by clinical and epidemiologic reports. When we first published our initial report on 'dopamine disorder in duodenal ulceration' in Lancet [92], we already cited the clinical observations not only that Parkinson's disease patients (who have dopamine deficiency) have excess 'peptic ulcers', but that after

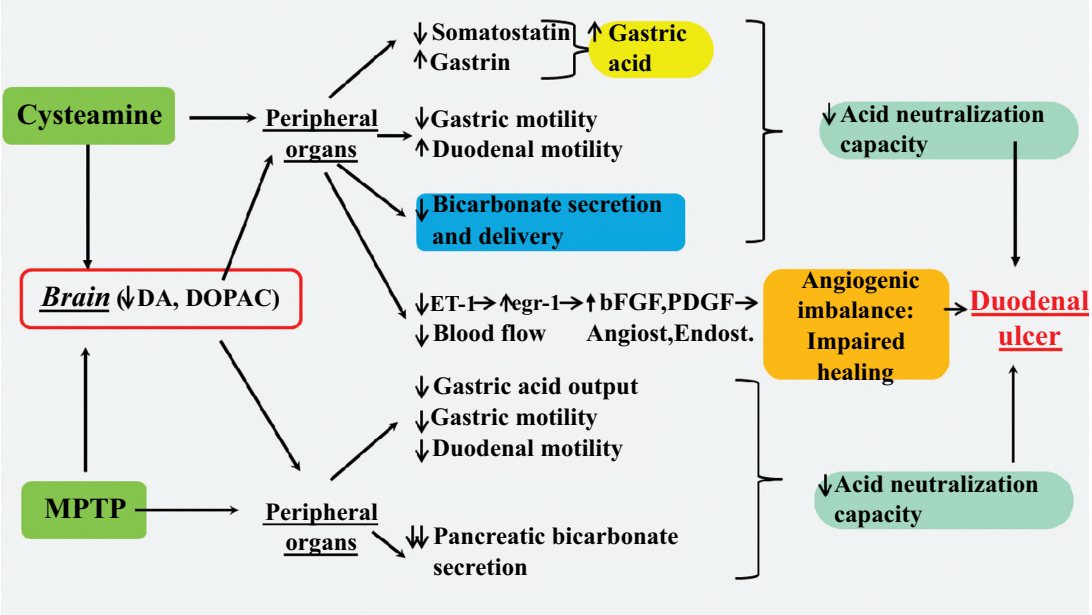

Fig. (8). Development of duodenal ulcers induced by cysteamine or the dopaminergic neurotoxin MPTP: These molecular mechanisms of the pre-ulcer stages duodenal ulceration could have been learned only from animal models!

treatment with L-DOPA (precursor of dopamine), the ulcer symptoms disappear… Furthermore, schizophrenics (with dopamine hyperactivity) are virtually immune to 'peptic ulcers', yet when treated with the dopamine antagonist haloperidol, often develop gastroduodenal ulcers [91,92].

Because schizophrenia is attributed, in part, to an overactive dopaminergic system, persons with schizophrenia may display a reduced susceptibility toward GI ulcers. A case-control study was conducted in patients represented in the 2002 National Inpatient Sample, the largest all-payer inpatient care database in the USA, consisting of 5 to 8 million inpatient hospital stays per year, which approximates a 20% sample of community hospitals [103]. A significant association was observed between schizophrenia and diminished risk for duodenal (odds ratio [OR] 0.55; 95% confidence interval [CI] 0.45-0.67) and gastric (OR 0.54; 95% CI 0.46-0.63) ($p < .01$) ulcers but not for gastrojejunal ulcers (OR 0.44; 95% CI 0.16-1.20) ($p = .11$). Potential confounders such as age, gender, race, tobacco or alcohol dependence, and H. pylori infection was controlled in multivariate analyses. This observational study in a large sample of patients in community hospitals suggests that schizophrenia and attendant neurobiologic mechanisms (*e.g.*, variability in dopamine pathways) may act in concert to modify the composite risk for gastrointestinal ulcers. Dopamine pathways warrant further prospective research as new potential drug targets in ulcer disease, as also mentioned in a recent short review article [104].

5. PREVENTION AND/OR TREATMENT OF ULCERS

Prevention is the most appropriate and economically attractive approach to any disease, esp., if etiologic prevention is feasible, like with the eradication of mosquitoes prevents malaria. Because of the complex etiology and pathogenesis of GI ulcers, etiologic prevention/treatment is rarely an option (Table **2**). As outlined in the above sections of this article as well as in the excellent and comprehensive review of Prof. Brozowski in this issue CPD [84], we know about a half a dozen endogenous substances that play an etiologic role and may be used for prevention of gastroduodenal ulcers, *e.g.*, PG, SH and other antioxidants, antacids, H_2S, CGRP, dopamine, but hardly any of these molecules can be used as drug

Table 2. Pharmacologic prevention and treatment.

- **Prevention:**
  - Pretreatment prevents GI lesions
- **Treatment/therapy:**
  - Treatment of existing lesions accelerates healing
  - Primary/Etiologic treatment removes the causative agent & let lesions heal automatically
  - Secondary/Therapeutic intervention accelerates healing

treatment of gastroduodenal ulcers. Actually, the whole concept and subsequent research of three decades of gastroprotection is related only to prevention and not to the clinically equally important, if not more critical treatment of chronic ulcers. Even central and peripheral dopamine that prevents gastroduodenal ulcers, seems to accelerate only the healing of experimental duodenal ulcers [92] and gastric ulcers [105].

Among the clinically used antiulcer drugs, antacids and antisecretory agents (both H_2 receptor antagonists and proton pump inhibitors – PPI) prevent gastroduodenal ulcers and by virtue of eliminating one of the etiologic factors, *i.e.*, gastric acid, they indirectly accelerate the healing of these ulcers. The new anti-H. pylori drugs do the same, *i.e.*, by elimination of this acid-resistant bacterium which decreases the bioavailability of gastric angiogenic growth factors that are essential for ulcer healing (see below). In the context of prevention and/or accelerated healing, three groups of molecules deserve analysis: angiogenic growth factors, sucralfate and BPC-157 (Table **3**).

5.1. Angiogenic Growth Factors

The first commercially available growth factor which stimulates the sprouting of new blood vessels from existing vessels, *i.e.*, angiogenesis, has been basic Fibroblast Growth Factor (bFGF), followed by Platelet-Derived Growth Factors (PDGF) and vascular

Table 3. Prevention and/or treatment of gastroduodenal ulcers.

- **Prevention only:**
  - Gastroprotective drugs (PG, SH, antioxidants)
  - "Adaptive gastroprotection"
- **Treatment only:**
  - Angiogenic growth factors (bFGF, PDGF, VEGF)
- **Treatment/therapy:**
  - New sucralfate
  - BPC-157/PL-10

endothelial growth factor (VEGF) [106]. bFGF was first isolated as a 'specific' peptide which stimulates the proliferation of fibroblasts [107], but soon afterward Folkman's lab identified it as a very potent stimulant of endothelial cell proliferation and tube formations, *i.e.*, of angiogenesis [108]. Compared to these angiogenic actions, the very first growth factor, *i.e.*, EGF (epidermal growth factor) stimulated only the proliferation of epithelial cell, with very little, if any, effects on fibroblast and endothelial cell proliferation (Table **4**).

Table 4. Comparative effects of EGF and angiogenic growth factors on gastroduodenal secretion, cell proliferation, and angiogenesis.

Peptides	Gs-acid	Du-bicarb.	Epith.↑	Fibrobl.↑	Angiog.
EGF	↓	↑	++	+/-	+/-
bFGF	-/↑	-	+	++	++
PDGF	-	-	+	++	+
VEGF	-	NT	-	-	++

The potent ulcer healing effect of angiogenic growth factors has been demonstrated in the rat cysteamine-induced chronic DU model, *e.g.*, daily gavage with bFGF and its acid stable mutant, starting on the third day after the experimental ulcers had developed, markedly accelerated the healing of experimental duodenal ulcers [109, 110]. Later, when PDGF-BB and VEGF became available for pharmacologic experiments, we could prove a similar, very potent DU healing effect of these peptides, administered daily in ng-µg ranges in rats with established cysteamine-induced duodenal ulcers [111-114]. Mechanistically, it is interesting that none of these peptides decrease gastric acid secretion – actually, bFGF enhances gastric acid output – yet the duodenal ulcers healed rapidly, because they also exerted potent angiogenic affects (Table **4**) that stimulated the creation of healthy granulation tissue at the ulcer site, over which adjacent epithelial cells migrated and covered the former ulcer crater. For comparison, EGF which has essentially no angiogenic effect, exerts antiulcer effects only by decreased gastric acid and enhanced duodenal bicarbonate secretion.

To assess the pharmacologic efficacy, the ultimate evaluation always comes from comparing the molar comparison of drugs that takes into consideration the size of the molecules, *i.e.*, the molecular weight. Thus, if we take into consideration the relatively small size (MW 252) of antisecretory drugs like cimetidine (Tagamet) and the large, multi-amino acid peptides like bFGF (MW 18,000), on molar basis, the ulcer healing properties of angiogenic growth factors are about 2-7 million times more potent than that of the antisecretory cimetidine (Table **5**).

Table 5. The molar comparison of antiulcerogenic doses of bFGF, PDGF, VEGF, and cimetidine in the rat model of cysteamine-induced chronic duodenal ulcer.

	bFGF	*PDGF*	*VEGF*	*Cimetidine*
Antiulcerogenic dose (/100g)	100 ng	500 ng	1 µg (1,000 ng)	10 mg (10^{10}pg)
Molecular weight	18,000	34,000	45,000	252
1 pmole	18 ng	34 ng	45 ng	252 pg
Antiulcerogenic dose in pmole/100g	5.6	14.7	22.2	39,682,540.0
Molar comparison	7,086.168	2,699.492	1,787.502	1

5.2. Sucralfate and its Derivatives

The prototype of non-PG gastroprotective drugs is sucralfate that was discovered in Japan before the first publication of 'gastric cytoprotective' action of low, non-antisecretory doses of PG derivatives [47, 48, 111]. Indeed, this mysterious wonder-drug without affecting gastric acidity, not only prevents the alcohol or NSAID-induced gastric lesions in experimental animals and in people, but it also accelerates the healing of gastroduodenal ulcers, irrespective of their etiologies [111, 114-116]. Initially, the molecular mechanisms of sucralfate actions were poorly understood, *e.g.*, ascribed to its mild stimulating action of gastric and duodenal bicarbonate as well as on gastric mucus secretion [111, 114] – never mind that the enhanced mucus secretion can be separated from gastroprotection, *e.g.*, PG also stimulate mucus secretion but if rats were pretreated with the SH antagonist N-ethylmaleimide, the gastroprotection is abolished without affecting the enhanced mucus out… [55]. Nevertheless, we learned by using components of the complex molecule of sucralfate, not only that its key component, the water soluble sucrose octasulfate, but inorganic sulfate also prevents ethanol and aspirin-induced gastric erosions [111, 116].

It was actually a serendipitous discovery *i.e.*, while working on the first angiogenic peptide bFGF to accelerate ulcer healing that we recognized that its sucrose octasulfate moiety, sucralfate actually resembles the sulfated heparins that were used to bind and extract bFGF and other angiogenic molecules [108, 111, 117]. Indeed, we found that sucralfate was very potent in binding bFGF and since sucralfate emulsion also sticks to the necrotic tissue in ulcer craters, it attracts and concentrates like a sponge angiogenic growth factors in and around the ulcer crater – where these peptides are most needed to heal the lesions [117, 118]. On the basis of these results with acute erosions and chronic ulcers, we proposed a new, molecularly clearly defined, "1 x 1 x1" mechanism of action of sucralfate [118]. Thus, since sucralfate resembles the natural sucrose, it has essentially no side effects and it does not interfere with the needed gastric acid section, yet it prevents and heals ulcers, we hope that the pharmaceutical industry will soon develop new, similar potent antiulcer dugs in the near future.

5.3. BPC-157

This intriguing peptide BPC, short of "Body Protecting Compound", discovered by Prof. Predrag Sikiric, and further characterized and tested by his large research team of basic and clinical investigators at the University of Zagreb [105, 119-122]. It was claimed that this 15 amino acid peptide was isolated from human gastric juice [105, 119]. A recent internet review [123] refers to it as a "healing miracle?" stating that "This amazing protein, BPC-157, is perhaps one of the greatest advancements in modern medicine I have seen in my life. It was developed to help with gastric ulcers and inflammatory bowel disease. But it does so much more! It can increase the healing of intestinal resectioning (*sic*) and reattach tendon to muscle and bone."

The structure of this pentadecapeptide BPV-157 (PL-10) is apparently Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val, MW 1419 [105, 119], its effect tested in many animal models and in a few clinical trials [119-122] but the challenge is that no gene match was identified for this peptide during the last about 20 years. Thus, accepting that it was isolated from human gastric juice, one would expect to be a 'natural product', yet no endogenous levels, receptors or its synthesizing cells have been published. Yet, as pharmacologic agent (*e.g.*, in µg and ng range in rats) is very potent and the achieved prevention and therapeutic results are apparently reproducible, based on publications originating from different laboratories, including our own [124-129].

Concerning erosions and ulcers in the GI tract, pretreatment of rats with BPC-157 prevented the acute gastric hemorrhagic erosions induced by stress or ethanol, the cysteamine-induced acute duodenal ulcers and its beneficial effect of BPC-157 "appears to be related to a strong endothelial protection" [121]. Not only it prevents various acute gastroduodenal lesions, but it also accelerates the healing, *i.e.*, if the peptide is administered after the induction of experimental gastric and duodenal ulcers [121, 126]. The peptide is also effective in the lower GI tract, *e.g.*, "BPC-157 reduces trinitrobenzene sulfonic acid-induced colonic damage in rats" [128] and the peptide reduced the severity of iodoacetamide-induced colitis in rats [127] as well as cysteamine-induced colitis even when complicated with colon-colon anastomosis [130].

The molecular and cellular mechanisms of these preventive and therapeutic actions are not clear, but it appears that in acute gastroprotection vasoprotection, *i.e.*, prevention of endothelial injury and maintenance of mucosal blood that allows the adjacent epithelial cells to migrate (restitution) seem to be the likely mechanisms. In the enhanced ulcer healing both in the upper and lower GI tract, stimulation of cell proliferation and the angiogenesis-dependent granulation tissue production appears to be key elements. Namely, in our *in vitro* studies [131], BPC-157 (PL-10) dose-dependently stimulated especially the proliferation of intestinal epithelial cells, much less potently the divisions of 3T3 fibroblasts and aortic endothelial cells. In our experimental ulcerative colitis experiments, the peptide enhanced angiogenesis and in tissue extracts we found increased expression of the transcription factor Egr-1 that regulates the expressions of angiogenic growth factors like VEGF, bFGF and PDGF [131]. Furthermore, BPC 157 affects NO-system [133] and several molecular pathways involved in the healing, including growth hormone receptors [134], cell proliferation and migration [135, 136], in part by enhanced expression of Egr-1 [131, 132].

Finally, the pentadecapeptide BPC-157, seems to be one of the rare drugs which not only prevent ulcerative lesions in both in the upper and lower GI tract, but it also enhances the healing of these lesions. Like dopamine [92, 137], this peptide is claimed to be of endogenous origin but further studies are needed to clarify its endogenous levels and origins as well as its receptors in all the organs where it's claimed to be exert beneficial effects.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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