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REVIEW ARTICLE

VASCULAR MEDIATION OF GASTRIC MUCOSAL DAMAGE AND CYTOPROTECTION

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Abstract : This review addresses questions surrounding the role of the mucosal circulation in damage and protection against chemical injury to the stomach. The modern history of the topic is briefly summarized, and widely used methods are appraised critically. The role of the circulation is examined in mucosal injury and in cytoprotection, and a new conceptual model is described which involves the vasculature and inflammatory mediators.

Key words : Gastric Mucosal Damage Cytoprotection Inflammation Gastric Circulation

GENERAL CONSIDERATIONS

The concept that gastric ulcerations and erosions have a vascular basis dates back to 1853, when Virchow proposed a circulatory mechanism for these mucosal lesions (1). This hypothesis held currency for a century, despite little or no clinical or laboratory evidence to uphold it. The historical papers on this topic have been reviewed previously (2,3). The modern history of this subject can be traced back about 25 years to research from Davenport's laboratory on disruption of the gastric mucosal barrier by topical damaging agents, leading to the back diffusion of H^+. Two observations relevant to a circulatory mechanism were: 1) severe degrees of damage to the canine gastric mucosa, caused by acidified aspirin, led to the appearance of erythrocytes or even frank blood in the gastric content (4), and 2) the venous blood draining such injured stomachs contained elevated concentrations of histamine (5,6). From these findings, Davenport proposed that the back diffusion of HCl into the mucosa caused release of stored histamine. The subsequent target of H^+ and histamine was the mucosal vasculature, which then became congested and lost its impermeance to macromolecules and erythrocytes. These insults to the local circulation resulted in the formation of edema and hemorrhage within the tissue (6). The vascular model for damage proposed by Devenport was imaginative, given the limited data from which it had sprung. With far more information available today, the current paradigm for a vascular basis in mucosal damage has not advanced greatly beyond his scheme.

About 15 years ago, Robert made the exciting discovery that several natural and synthetic prostaglandins, administered in advance to rats, prevented gross evidence of mucosal injury by a variety of dissimilar topical damaging agents, such as indomethacin, aspirin, and taurocholate, and even protected the mucosa against necrotizing interventions, such as topical applications of absolute ethanol or boiling water (7-10). This nearly magical property of some prostaglandins, termed "cytoprotection", begged for an explanatory mechanism. Not surprisingly, many investigators began to explore a circulatory basis for cytoprotection, inasmuch as the first evidence for this unique property of prostaglandins was their prevention of bloody streaks, which appeared on the mucosal surface of rat stomachs exposed to injurious agents.

The results of subsequent explorations into

the mechanism of gastric cytoprotection by prostaglandins have yielded several important pieces of information and insights. Better methods have been developed for measuring gastric mucosal blood flow and for defining injury and protection in the stomach. A large array of cytoprotective agents, other than prostaglandins, have been identified. Injury to the mucosal circulation and cytoprotection against damage, are being viewed in terms of cellular pathophysiology. The purpose of this review is to examine these recent developments and to speculate on likely areas for future research.

METHODOLOGY

For several years after the discovery of prostaglandin cytoprotection of the gastric mucosa, investigations of a circulatory mechanism were limited to estimating mucosal blood flow by the clearance of aminopyrine (11,12) and to estimating damage to the mucosa by gross inspection of its surface (7-9). Four more sophisticated estimations of mucosal blood flow have come into wide use in the past decade, namely radiolabelled microspheres, hydrogen gas clearance, laser Doppler velocimetry, and in vivo microscopy. Unfortunately for research on gastric mucosal circulatory involvement in damage and cytoprotection, these newer methods suffer from serious limitations, of which investigators need to be aware. None of these techniques appears to satisfy all of the requirements of an ideal method for measuring blood flow (13).

With the radiolabelled microsphere method, spheres of about 10 micron diameter are injected into the left ventricle and are distributed with the cardiac output to the organs and tissues of the body, along with the blood (14). Their size is such as to assure their being trapped by the capillaries of each tissue. An independent measure of blood flow is established by aspirating blood containing the radioactive spheres from a major artery at a known rate of removal and counting the radioactivity of the sample (15). A sample of tissue or the whole organ is removed at the end of the experiment, and its radioactivity is counted to allow calculation of blood flow. The problems with this method include (16,17): 1) finding in the gut that all spheres in the mucosa pass through the submucosa, thereby precluding a separate measure of mucosal blood flow, i.e., the radioactivity is reflective of both tissues; 2) the finding that a small change in sphere size yields large changes in the number of spheres trapped in the capillaries of the mucosa and in the localization of spheres within the mucosa; 3) the finding that increases in arterial pressure during an experiment can dislodge spheres and force them out of the capillaries; and 4) the limited number of measurements (up to 6) that can be made with the technique render it insensitive to dynamic circulatory events occurring over brief time periods.

The hydrogen gas clearance measures mucosal blood flow at a point on the mucosa (18-19). The method involves having an animal breathe a 3% H_2 gas/air mixture for 30 minutes to saturate the gastric mucosa with H_2. Then, the animal breathes only air and the H_2 content of the gastric mucosa declines as a monoexponential decay curve, presumably because the dissipation of H_2 from the tissue is caused solely by a steady blood flow carrying off the molecular hydrogen. A platinum electrode inserted into the mucosa, and connected to a polarograph, measures the current generated by conversion of molecular hydrogen into hydrogen ions, which reflects the concentration of molecular hydrogen in the tisue. The problems inherent with this technique include (17): 1) the electrode is in contact with a nearly infinitesimal fraction of the mucosa, which is presumed to be representative of the entire tissue and which, therefore, presumes a nearly homogeneous mucosal blood flow; 2) each measurement takes more than 30 minutes to accomplish, which limits the number of observations per experiment and is not applicable to the measurement of more rapid changes in mucosal blood flow; 3) the validation of this method was made by comparison with the radioactive microsphere technique. As noted above, the latter method is hardly a gold standard for the estimation of mucosal blood flow.

The laser-Doppler method of measuring tissue blood flow relies on delivering a laser beam through

a fiberoptic cable to the mucosal surface, through which blood is flowing and from which the beam is reflected (20-22). A nearby sensor is responsive to shifts in the frequency of backscattered light, which is recorded as a current. The frequency of the reflected electromagnetic wave is proportional to the velocity of blood flowing through the tissue. This method is sensitive to rapid changes in mucosal blood flow and has been shown to correlate well with simultaneous measurements of total visceral organ blood flow, using an independent method (20,23). The problems with this technique are not inconsequential, however. Measurements obtained with the laser-Doppler velocimeter are not presented in units of blood flow per gram of tissue, inasmuch as the current generated reflects the velocity of blood perfusing an unknown mucosal mass. Hence, the instrument measures moment-to-moment changes in tissue perfusion, assuming a linear relation between its measurements and actual blood flow in the mucosa at the site of measurement (17). This method is supposed to measure changes in the velocity of blood flowing through a cubic millimeter of tissue lying beneath the probe; in a dog stomach such a volume of tissue would probably still be within the mucosa, but in a rat stomach this volume might include much extramucosal tissue. Furthermore, like the hydrogen gas clearance method, the site of measurement is a minuscular proportion of the total surface area of the gastric mucosa. Implicit in these two methods is the unproven assumption of representationalism of measurements during damage and cytoprotection. Estimations of mucosal blood flow with laser-Doppler velocimetry would be more reliable if the method were calibrated by hydrogen gas clearance twice during each experiment, i.e., during control conditions and after a stable state had occurred with the experimental perturbation. It is to be hoped that future engineering developments with this device will include either a computerized scanning capability to allow the instrument to encompass much larger portions of mucosal surface area or multiple probes and sensors to permit simultaneous measurements from various mucosal sites.

In vivo microscopy relies upon delivery of intense, cold light via fiberoptic rods to the serosal surface of the stomach, thereby transilluminating mucosal blood vessels for viewing with a specialized microscope (22,24). The observational system is connected to a videocamera for purposes of measurement and recording on tape. With this technique it is feasible to measure changes in the diameter of a microvessel and changes in the velocity of erythrocytes passing through the vessel. From such measurements, blood flow can be determined in an isolated capillary, or responses of different microcirculatory vessels can be observed. Using fluorescent compounds, which bind to albumin or to injured endothelial cells after introduction into the circulation, it is possible to recognize an increase in capillary permeability or the occurrence of endothelial damage. The limitations of this method are: 1) the presumed representationalism of the sampling site, which cnsists of a few microcirculatory vessels out of millions in the mucosa; 2) the limitation of the method to observation of blood vessels in the superficial third of the mucosa (against a potent damaging agent, cytoprotection is most evident in the deeper 2/3 of the mucosa); and 3) the technical difficulty of discriminating the margin of the vascular wall for purposes of determining changes in vessel diameter (which is essential for the estimation of blood flow in the vessel).

Finally, delineation of damage to the mucosa has been a troublesome matter for investigators. Initially, mucosal damage and protection against damage were diagnosed mainly by the presence or absence of bloody streaks on the epithelial surface of stomachs exposed to a noxious intervention (8,9). It was subseqently found that intervening areas between the bloody streaks were also damaged, and that badly damaged sites on the epithelium were covered by migrating epithelial cells from the pits in a matter of minutes after exposure to the injurious agent (25,26). With more rigorous use of histological examination, recent reports indicate severity of mucosal injury in terms of the following degrees of damage (22,24,27):

1. mild - vacuolization of the cytoplasm and nuclear damage plus loss of cell-to-cell integrity restricted to the superficial epithelium;

2. moderate - the foregoing plus cellular damage or cell death in the deeper portions of the pits and congestion of the deeper mucosal microcirculation; and
3. severe - all of the foregoing plus damage or death evident deep in the mucosa among oxyntic and peptic cells, widespread edema, and extravasation of erythrocytes into the extravascular compartment.

Furthermore, the degree of damage is also rated in terms of the proportion of the mucosal surface area which is injured. With necrotizing agents more than a third of the surface area is affected. In the future, it is likely that fluorescent probes will be used to identify specific enzyme systems which are impaired or stimulated, membranes of the cell and its organelles which are rendered more permeable, intracellular ion localizations and pH changes, cytosolic volume alterations, DNA aberrations, and cytoskeletal responses, to name some of the probable subcellular targets of mucosal cytotoxicants.

THE DAMAGED MUCOSA

Experimental damage to the gastric mucosa can be defined in terms of its severity. Slight degrees of damage are detected by functional changes in membrane permeability to transported ions. Severe degrees of damage are described in terms of structural alterations of the mucosa and other evidence of tissue pathology, such as edema and hemorrhage. The generally accepted and earliest sign of damage to the mucosa, following exposure of its epithelial surface to a topically applied, noxious chemical, has been a decrease in the magnitude of the electrical potential difference (PD) across the mucosa (6,28). The assumption made from this finding is that the decrease in PD clearly reflects a loss of impermeability of the epithelial lining of the mucosa to ions, such as H^+, Na^+, and K^+. It should be noted, however, that a loss of PD could also result from a decrease in activity of the electrogenic chloride pump or an increase in active transport of protons into the gastric lumen, as would occur during stimulation of oxyntic cell secretion of acid by an exogenously administered secretagogue (29). The assumption that a decrease in transmucosal PD signifies early evidence of injury is more credible if simultaneous measurements of the gastic content reveal an increased flux of H^+ from lumen to tissue and an increased concentration of Na^+ and K^+ in the lumenal fluid (6,30).

There are a number of pathophysiological events which have been found following exposure of the mucosal surface to a topically applied, potent damaging intervention (22,23-28,30-40). These events are depicted in Figure 1. It appears that application of a high concentration of acidified ethanol, for example, kills the epithelial cells, thereby prompting diffusion of both ethanol and H^+ into the mucosal substance. The invasion by these foreign agents provokes the release of endogenous mediators, such as histamine from mast cells. Submucosal venospasm, vascular congestion, and stasis of mucosal blood flow ensue. Mucosal capillary permeability to macromolecules increases with histamine, leading to the formation of edema. Capillary endothelial cells are damaged, and there is extravasation of red blood cells into the extravascular compartment, which constitutes tissue hemorrhage. Reconstitution of the mucosal lining by epithelial cells migrating up from the pits occurs in response to the injury. The end result

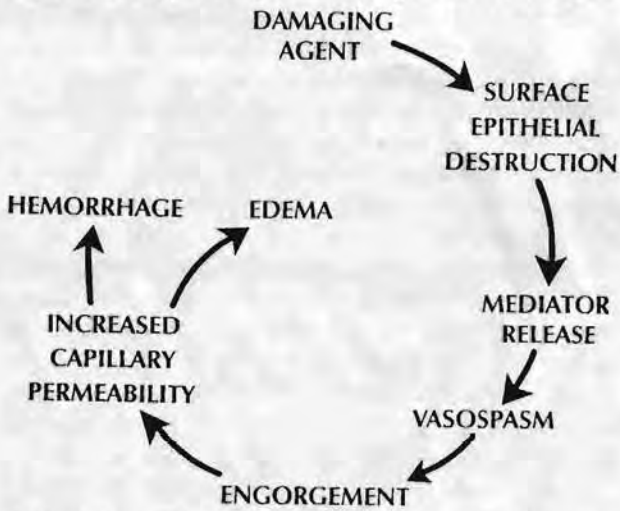

Fig. 1 : The traditional vascular model for mucosal damage. The events depicted are presumed to be sequential and caused by the preceding event.

of this train of pathophysiological events is widespread cell death. With necrotizing insults to the unprotected epithelial surface, even peptic cells in the deepest third of the mucosa are killed, and more than a third of the mucosal surface has been badly injured.

The rapidity of the foregoing events in damage is remarkable (22,24,27,32,33). Epithelial cell death at the point of contact on the surface with a topically applied poison is nearly instantaneous. Invasion of the mucosa by acid and ethanol commences within seconds. Venoconstriction in the submucosa occurs in less than one minute, and there is evidence of increased capillary permeability in less than 2 minutes after initial exposure to a severe damaging intervention.

The preceding description of severe injury to the gastric lining has sufficient substantiation from reports in the literature to convince a skeptic that the mucosal circulation is involved in mucosal damage. However, that point was really resolved by Davenport and Robert many years ago. The unresolved question is whether or not the mucosal circulation plays a sole or overriding role in the cascade of pathophysiological events leading to massive cellular necrosis in the mucosa. Is circula tory derangement the common pathway for all damaging interventions in the stomach? There is some evidence that supports a skeptical answer to the question.

One consideration of importance in assessing the primacy of circulatory derangements in mucosal damage is the array of experimental interventions which have been employed to provoke gastric mucosal damage, erosions, or ulcerations. The list in Table 1 is not exhaustive but is sufficient large to make the point that these injurious substances are rather dissimilar chemically and even more heterogeneous pharmacologically. Indeed, their only obvious common action is that they damage the gastric mucosa. Among this diverse collection of noxious materials are some simple inorganic chemicals, i.e., hypertonic solutions of either HCl or NaOH, and even more non-specific insults to living tissue, i.e., boiling water or absolute ethanol.

TABLE I : Some Interventions Which Provoke Gastric Mucosal Damage, Erosions, or Ulcers.

Aspirin	PAF
Indomethacin	Ethanol
Prostaglandin Antibodies	Histamine
Hypertonic HCI or NaOH	Acetylcholine
Digitoxin	Vasopressin
Boiling Water	Endothelin-1

It would require some stretch of the imagination, plus rather unequivocal evidence, to presume that the mucosal response to this range of injurious interventions is restricted to an intial local circulatory collapse before other tissue systems malfunction and other cells can be mortally damaged. With respect to this latter point, it should be noted that the death of the surface epithelial cells, to which absolute ethanol has been applied, takes place almost instantaneously or within a few seconds at most; such timing precludes ischemia as the essential and immediate lethal event preceding epithelial cell death. Furthermore, we have yet to establish the comparability between the spectrum of mucosal responses to a topically applied necrotizing agent and the responses to short-term, severe ischemia (41-43).

There are also paradoxes about mucosal prostaglandin synthesis in the damaged stomach, which are not easily reconciled. Thus, administration of aspirin to rats in a dose of 25 mg/kg reduced gastric mucosal prostaglandin synthesis by as much as 95% and administration of mepirizole in a dose of 100 mg/kg reduced mucosal prostaglandin synthesis comparably, yet neither agent appeared to damage the stomach (44,45). Conversely, topical application of 60% ethanol to the human gastric mucosa caused damage but did not decrease prostaglandin synthesis (46). It is, of course, possible that damage involves metaboliteis other than the products of the cyclooxygenase system.

Well over 95% of the mucosal mass consists of non-vascular cells (oxyntic cells, peptic cells, epithelial cells, visceral muscle cells, and other cell types of the lamina propria, gastric glands, and non-vascular compartment). Many of these cells

bear the brunt of a necrotizing insult before the circulation is affected. Given the non-specific nature and overwhelmingly destructive effects of some experimental interventions used to damage the gastric mucosa, it may well be that the tissue response is also non-specific. Few cells close to the epithelial surface escape the injurious effects of the topical application of a necrotizing intervention, even in the face of a cytoprotective drug.

CYTOPROTECTION

Cytoprotection is a term which has been applied to the ability of a sizeable and growing number of exogenously administered drugs and chemicals, and other experimental manipulations to reduce the extent of subsequent mucosal injury by a known damaging intervention. Inasmuch as the subject of injury is the acid-secreting mucosa, cytoprotection has to be demonstrated in the absence of inhibition of acid secretion by the putative cytoprotective agent. Although cytoprotection is regarded as a pharmacological or exogenous event, its existence raises the question of a possible physiological counterpart for two reasons. First, the minimal dose of some agents required for protection is exceedingly small, approaching that required to match tissue levels of the same chemical. Second, at least three of the known classes of cytoprotective agents are chemical species which also occur naturally in the gastric mucosa, namely E and I types of prostaglandins, sulfhydryl donors, and sensory neuropeptides. These findings suggest the possibility of multiple metabolic avenues by which cytoprotection may be realized, even as there may be multiple ways in which to damage the gastric mucosa.

To the extent that mucosal damage involves the circulation, protection against such injury also bestows beneficial effects on the gastric vasculature. However, ascribing a circulatory mechanism to cytoprotection implies clearly that cytoprotective drugs act first and foremost on the blood vessels of the mucosa to enhance the resistance of the vasculature to the damaging intervention.

The most obvious circulatory function which might be protected in the face of tissue injury is blood flow through the microcirculation. As noted previously under METHODOLOGY, there are limitations with each of the various techniques which have been used to arrive at an estimation of mucosal microcirculatory flow. Another microcirculatory parameter, which has been assessed, is capillary impermeability to the macromolecules of the plasma. In the near future, it is likely that endothelial function and the behavior of neutrophils and erythrocytes will be measured during gastric mucosal damage and cytoprotection, as has occurred with ischemia/reperfusion injury of the gut.

The ability of cytoprotective agents to prevent or ameliorate adverse circulatory responses to damaging interventions has been amply documented in numerous reports. Exogenously administered prostaglandins (7-10,22,24,30,31,39,47,48), stimulation of mucosal synthesis of prostaglandins (38,46,49-51), and cytoprotectants unrelated to prostaglandins (22,52-63) have been observed to prevent or reduce submucosal venular constriction, vascular congestion, capillary leakage, and tissue hemorrhage provoked by topically applied, damaging substances. Thus, for example, topically applied 75% ethanol caused mucosal injury but did not prompt a cessation of microcirculatory blood flow; addition of indomethacin to the damaging regimen aggravated the injury and provoked a stasis of blood flow; and pretreatment with an analog of prostaglandin E_1 ameliorated the injury and maintained microcirculatory blood flow, despite subsequent treatment with ethanol and indomethacin (31).

The unresolved matter is the same for cytoprotection as for damage. How important is the maintenance of circulatory function? Is circulatory maintenance the earliest, pivotal part of the mucosa which is protected? In cytoprotection, there is a nearly inseparable association between protection of the mucosal microcirculation and protection of the rest of the mucosa against the more severe ravages of damage. However, this close association does not prove causality in either direction nor does it establish circulatory protection as the *sine qua non* for gastric mucosal cytoprotection.

Many chemically and pharmacologically different cytoprotective agents have been described since Robert's initial reports about certain prostaglandins possessing protective properties against damaging substances in the gastric mucosa. A limited list of these agents appears in Table II. The left hand column cites exogenously administered prostaglandins and agents which have been shown to increase biosynthesis of endogenous prostaglandins in the gastric mucosa (38,49,50-52). Thus, for example, depletion of mucosal glutathione with dimethyl maleate prompted increased mucosal production of prostacyclin and prostaglandin F_2 alpha, while decreasing the synthesis of leukotrienes (38). However, the cytoprotectants listed in the right hand column have been found not to turn on endogenous synthesis of prostaglandins (22,53-63). Thus, the increased presence of prostaglandins in the mucosa does not appear to be a prerequisite for protection.

TABLE II : A List of some Cytoprotectants.

Prostaglandins	Afferent Nerve Peptides
Sucralfate	Dopamine
IVC Neurotensin	Phenylethylamine
Zinc Sulfate	Acetaminophen
Glutathione Depletion	Sulfhydrils
Colloidal Bismuth Subcitrate	Carbenoxolone

Further scrutiny of the list is also instructive, with regard to a possible beneficial circulatory mechanism underlying cytoprotection, such as increasing mucosal blood flow. Exogenously administered prostaglandins of the D, E, and I types have been shown to possess vasodilator activity (11, 64-67). However, the cytoprotective dose of prostaglandin is usually only a small fraction of its vasodilator dose. When administered in its cytoprotective dose, 16, 16- dimethyl prostaglandin E_2 was found to decrease mucosal blood flow (22, 47, 68). The agent did not increase the diffusion of ethanol away from the gastric mucosa, again indicating that this protective drug was not increasing blood flow through the tissue (69). In preliminary work, Guth and his co-workers have also found that cytoprotective doses of 16, 16-dimethyl prostaglandin E_2 increase capillary permeability to macromolecules, hardly a beneficial circulatory effect for a known cytoprotectant. Furthermore, prostaglandin F_2 alpha is a potent vasoconstrictor drug (70, 71), although it is cytoprotective (71). Afferent nerve stimulation with capsaicin releases vasodilator neurotransmitters (54-56), but phenylethylamine is an alpha adrenergic agonist with vasoconstrictive actions (53). Other agents on the list are not direct-acting, vasoactive drugs. The foregoing information does not support the concept that an increased mucosal blood flow is a requisite property of a protective drug. Indeed, damaging concentrations of topically applied ethanol prompt an increase in blood flow (48,72) and an increase in mucosal synthesis of prostaglandins (73).

TOWARDS A NEWER MODEL

A great deal of exciting, new information has become available in the last few years about mucosal responses to damage and the critical roles of local mediators of inflammation (74-82). Much of this information relates to ischemia-reperfusion injury of the mesenteric or other circulations. Application of some of this information to the injured gastric mucosa and incorporation of previosuly discussed information is presented in Figure 2 as a new model for damage and cytoprotection. Injury to the gastric mucosa with a topically applied agent, such as high concentrations of ethanol, rapidly kills epithelial cells and disrupts their integrity as a relatively impermeable sheet membrane. Both the damaging agent and gastric acid penetrate into the mucosa. Several cell types are victimized by the noxious invaders, including microvascular and non-vascular types of cells. Interstitial mast cells degranulate, releasing histamine, leukotrienes B_4 and C_4, and thromboxane A_2. Capillary and venular endothelial cells release a chemotactic factor for neutrophils, as well as endothelin-1 and platelet activating factor. Neutrophils attached to endothelial cells generate myeloperoxidase, elastase, and nitric oxide, and are stimulated to metabolize xanthine into oxygen free radicals. In damaged cells lysosomes release proteases. This array of inflammatory mediators is unleashed on the already damaged mucosa and causes digestion of protein and peroxidation of lipids in cell membranes, con-

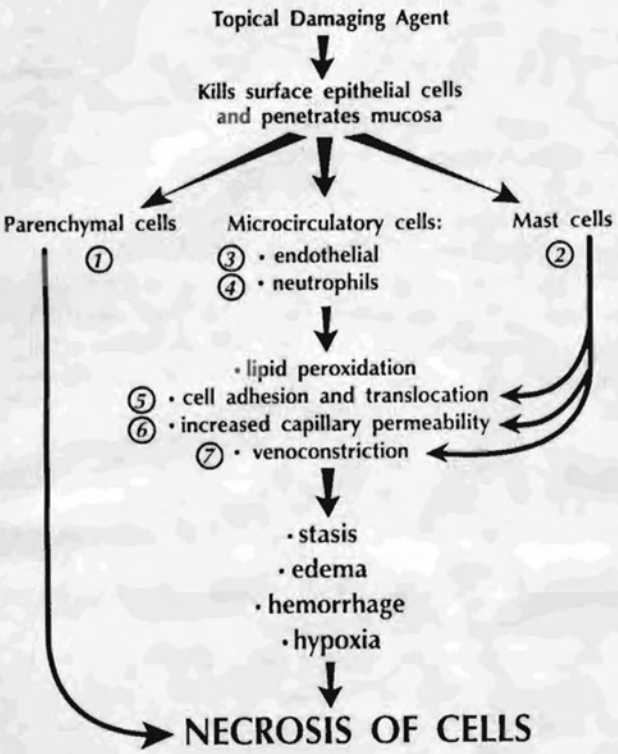

Fig. 2 : Sequence of damage and sites of cytoprotection. A more sophisticated concept of damage is presented. Circled numbers identify steps in the pathophysiology of chemical injury at which cytoprotective interventions have been successful in ameliorating the extent of damage to the mucosa.

striction of venules, obstruction of capillaries, focal hypoxia, extravasation of macromolecules and fluid into the extracellular space, and translocation of erythrocytes and neutrophils from the blood into the tissue. The culmination of this acute pathophysiological catastrophe is focal necrosis of the mucosa, extending to the inner third of the tissue, with the death of nearly all parenchymal cells in its wake. The sites at which cytoprotective agents may obviate deep tissue necrosis appear to be numerous. Prevention of the demise of the germinal epithelium in the gastric pits permits rapid reconstitution of the denuded epithelium (22,25,28). Some cytoprotective prostaglandins stabilize lysosomal membranes and prevent proteolysis of subcellular structures (80). Other important protective actions may include increasing the resistance of cell membranes to peroxidation and the scavenging of oxygen free radicals (81). Clearly, in this devastating array of profound cellular insults, the maintenance of a nearly normal perfusion of capillaries and the maintenance of their relative impermeability to erythrocytes, neutrophils, and macromolecules are critical requirements for survival of mucosal cells. However, maintenance of the circulatory function is not the only requirement of such survival. Furthermore, ischemia *per se* must be extreme and protracted to threaten the viability of the gastric mucosa (41-43). As noted previosuly, important elements of damage and necrosis occur within a minute or two following topical application of the noxious agent, well before death from ischemia could have occurred. Central to this new line of explorations is the assumption that the gastric mucosal reponse to chemical injury is much the same as its response to ischemia/reperfusion injury. An implication of this assumption is that there is a great deal of restriction on the range of tissue reactions to all forms of injury. The foregoing assumption has not been fully tested, however.

In conclusion, derangement of circulatory function is an important element of experimental damage to the gastric mucosa, and cytoprotective agents ameliorate a considerable part of the circulatory expression of damage. Both damage and cytoprotection involve more than the blood vessels of the mucosa, however. Future research will be required to delineate the spectrum of these multifactorial events.

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