Volume 18
Number 1

A Comparative Study of the Inhibitory Action of Chemical Agents on Peptic Activity

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PEPTIC ULCER is attributed to an excess of hydrochloric acid and pepsin in gastric juice (1, 2, 3). Ulceration of the gastro-intestinal tract by physiological concentrations of hydrochloric acid has never been produced in the absence of pepsin (4). Shock and Fogelson (5) demonstrated the significance of the pepsin factor in histamine produced ulcers.

It would therefore follow that in the treatment of peptic ulcer any compound which inhibited the action of pepsin should exert a beneficial effect. Numerous studies have been made of inhibition of the action of pepsin through the use of physical and chemical means; the results obtained are presented in summary (Table I).

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Submitted June 14, 1948.

TABLE I

Compound	Concentration	Amount of Inhibition	Reference
Amino-monocarbonic Acids	Equal to HCl	50%	(7)
Egg Albumin		None	(8)
Proteoses	5%	Absolute	(8)
Gelatin	10%	Stops Proteolysis	(8)
Carbohydrates, Fat		Nil	(8)
Alcohol	32%	No Digestion	(8)
Benzoic Acid	1%	Absolutely Inhibitive	(8)
Sodium Benzoate	1%	Absolutely Inhibitive	(8)
Boric Acid, Sodium Borate		Nil	(8)
Salicylic Acid	Small Amounts	Distinctly Inhibitory	(8)
Sodium Sulphite	1:100	Prevents Proteolysis	(8)
Potassium Nitrate	1:400	Inhibits Proteolysis	(8)
Creosote		Strongly Inhibits	(8)
Glucose, Levulose, Galactose, Sucrose, Maltose, and Lactose	Dilute	Stimulates Peptic Digestion	(9)
Glucose, Levulose, Galactose, Sucrose, Maltose, and Lactose	Concentrated	Inhibit	(9)
Paraformaldehyde, Phenol		Inhibit	(10)
Sodium Chloride, Neutral Salts	2.5%	Complete Inhibition	(11)
Bile Acids		Inhibit	(12)
Alkali	pH 6	Enzyme Destroyed	(13)
Filter Paper Pulp	10 gm. in contact with pepsin solution	Varied with paper and concentration of pepsin	(14)
Aliphatic Acids		Inhibition	(15)
Unsaturated Aliphatic Acids		More pronounced Inhibition	(15)
Animal Charcoal	pH 1 to 2	Best Adsorption	(16)
Salicylic Acid		Inhibited	(17)
Aspirin		Inhibited to Less Degree	(17)
$Ca_3(PO_4)_2$		Pepsin Readily Adsorbed	(18)
Bi-Quinine Compound			
8 $BiI_3.2C_{20}H_{24}N_2O_2.HI$	10% Bi	Retards Action of Pepsin	(19)
$BiOH(NO_3)_2.5CS(NH_2)_2$	.0134% Bi	Retards Action of Pepsin	(19)
Zinc Sulfate	Low Concentration	Retards Action of Pepsin	(20)
Magnesium Sulfate	High Concentration	Retards Action of Pepsin	(20)
Cotton		Removes Pepsin from sol'n.	(21)
Edestin, Melon Globulin		Form Insoluble Complex With Pepsin	(22)
Iodine	34-40 Mols I/Mol. Pepsin	99%	(23)
Phloroglucinol	High Concentration	Inactive	(24)
Phenol	High Concentration	Inhibits	(24)
o-Cresol, m-Cresol, p-Cresol	High Concentration	Inhibits More Than Phenol	(24)

TABLE I (Continued)

Compound	Concentration	Amount of Inhibition	Reference
Pyrocatechol	High Concentration	Inhibits at High Concentration	(24)
Hydroquinone	High Concentration	Inactive	(24)
Resorcinol, pyrogallic Acid	High Concentration	Inhibits at High Concentration	(24)
Guaicol	High Concentration	Inhibits More Than Phenol	(24)
Veratrole	High Concentration	Inhibits More Than Phenol	(24)
Zephiran (Cationic Detergent)	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Igepon AP	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Aerosol OT	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Intramine (Anionic Detergents)	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Doxad Nos. 11, 21 ,23 (Anionic Detergents)	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Arctic Syntex A	150 mg/50 cc. Gastric Juice	No Inhibition	(25)
Tergitol-7 (Anionic Detergents)		Decrease Peptic Activity Moderately	(25)
Actival (Anionic Detergents)		Decrease Peptic Activity Moderately	(25)
Duponal P. C. (Anionic Detergents)		Inhibit Peptic Activity Markedly	(25)
Nacconale (Anionic Detergents)		As Effective as Sodium Alykyl Sulfate	(25)
Sodium Decyl Sulfate		Most Effective of the Alkyl Sulfates in lowering Peptic Activity	(25)
Sodium Dodecyl Sulfate		Most Effective of the Alkyl Sulfates in lowering Peptic Activity	(25)
$CaCO_3$, $Al(OH)_3$		Inhibition	(26)
Sodium Lauryl Sulfate	100 mg.	No Inhibition	(26)
Sodium Lauryl Sulfate	200 mg.	Decrease in Activity. If pH Remained Unchanged No Inactivation Occurred	(26)
Na Alkyl Sulfate		Inhibits in Absence of Lipids	(27)
$CaCO_3$, $Al(OH)_3$, $Mg(OH)_2$		Caused Decreased Peptic Activity Simultaneously with a Rise in the pH of Gastric Contents	(28)
Na Lauryl SO_4		Caused Decreased Peptic Activity Simultaneously with a Rise in the pH of Gastric Contents	(28)
p-Chloro, o-Chloro, and p-Bromo Phenol	All Equal	Most Active Inhibitor	(29)
p-Nitro Phenol	All Equal	↕	(29)
p-Amino Phenol	All Equal	↕	(29)
Phenol	All Equal	↓ Least Active	(29)
Inverted Palmitic Acid		Pepsin Adsorbed	(30)
Inverted Cetylamine		Pepsin Adsorbed	(30)
Ultraviolet Light		Deactivates Pepsin	(31)
$Al_2(OH)_6$, $AlPO_4$, and $AlCl_3$		Inactivate Pepsin	(32)
$Mg_2Si_3O_8$ $25H_2O$		No Inactivation	(32)
Cl, NaOCl, I	15-65 Milli-Equiv. per Liter of Hydrolyzable Medium	Inhibited Profoundly	(33)
Na Lauryl Sulfate		Completely Inhibited	(34)
$CaCO_3$, $Al(OH)_3$		Inhibited $Al(OH)_3$ is better than $CaCO_3$	(35)
Na Alkyl Sulfate		Markedly Inhibits Peptic Activity	(36)
Na Alkyl Sulfate		When administered in conjunction with a diet low in fat — peptic activity is decreased.	(37)

EXPERIMENTAL

In this study it was decided to determine the effect of substances of varying chemical nature on peptic activity independent of change of pH. A comparative study was made of the inhibitory action of these substances on the digestion of coagulated egg albumin in vitro with a hydrochloric acid solution of 1:3000 N. F. Pepsin. The measurements were made by the method of Mett (6). The substances tested either proved indifferent or tended to check digestion. Where the substance tested was insoluble in the hydrochloric acid solution of pepsin, the mixture was shaken mechanically for 30 minutes. In each case where a mixture resulted, the peptic activity was determined on the supernatant liquid as well as on the heterogeneous mixture. The pH was held constant by adjustment with hydrochloric acid to pH 1.5 to 1.6 in order to obviate any effect caused by change away from the optimum for digestion of the egg albumin by the test substance. An aliquot of the mixture or solution after adjustment of the pH to 1.5 was then used to determine the activity of the residual pepsin. The volume of test solution or mixture in contact with Mett tubes was five cc. The results obtained are listed in Table II.

TABLE II

Substance Tested	Concentration mg/5 cc.	Conc. 1:3000 N. F. Pepsin mg/5 cc.	% Inhibition (Heterogeneous Mixture)	% Inhibition (Supernatant Liquid)
1. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	15	1.5	89	99
2. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	13	1.5	61	75
3. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	10	1.5	50	79
4. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	5	1.5	41	50
5. Insoluble Polyamine Anion Exchange Resin A, Commercial Sample 200 Mesh	2	1.5	30	30
6. Insoluble Polyamine Anion Exchange Resin B, Commercial Sample 200 Mesh	15	1.5	95	100
7. Insoluble Polyamine Anion Exchange Resin C, Commercial Sample 200 Mesh	15	1.5	100	100
8. Insoluble Polyamine Anion Exchange Resin D, Commercial Sample 200 Mesh	15	1.5	65	100
9. Cation Exchange Resin A, Hydrogen Activated Commercial Sample-200 Mesh	15	1.5	26	None
10. Cation Exchange Resin B, Hydrogen Activated Commercial Sample-200 Mesh	15	1.5	40	40
11. Cation Exchange Resin C, Hydrogen Activated Commercial Sample-200 Mesh	15	1.5	49	49
12. Cation Exchange Resin D, Sodium Activated Commercial Sample-60 Mesh	15	1.5	75	44
13. Synthetic Sodium Aluminum Silicate-200 Mesh	15	1.5	0	75
14. Activated Bauxite (Essentially Al_2O_3)	15	1.5	88	94
15. Fullers Earth (Essentially SiO_2)	15	1.5	99	99
16. Synthetic Magnesium Silicate	15	1.5	75	94
17. Activated Charcoal	15	1.5	100	100
18. Diatomaceous Earth	15	1.5	19	19
19. Bauxite	15	1.5	44	58
20. Magnesium Trisilicate	15	1.5	84	84
21. Filtrol Adsorbent	15	1.5	88	84
22. Yeast Protein Hydrolysate	32	3.0	—	86
23. Lactalbumin Hydrolysate	40	3.0	—	88
24. Methionine	16	3.0	—	56
25. Glycine	16	3.0	—	78
26. Sulfonated Product of Fatty Acids and Aliphatic Compounds (Anionic Detergent)	15	1.5	—	84
27. Decyl Benzene Sodium (Anionic Detergent)	15	1.5	—	75
28. Cetyl Dimethyl Benzyl Ammonium Chloride (Cationic Detergent)	15	1.5	—	19
29. Sodium Oleate (Anionic Detergent)	15	1.5	100	—
30. Bentonite	15	1.5	100	100
31. Bentonite	10	1.5	100	100
32. Bentonite	6	1.5	100	100
33. Bentonite	4	1.5	99	99
34. Bentonite	2	1.5	61	83
35. Sodium Alkyl Sulfate, Principally Lauryl	15	1.5	100	100
36. Sodium Alkyl Sulfate, Principally Lauryl	10	1.5	—	100
37. Sodium Alkyl Sulfate, Principally Lauryl	5	1.5	—	100
38. Sodium Alkyl Sulfate, Principally Lauryl	2	1.5	—	100
39. Sodium Alkyl Sulfate, Principally Lauryl	1	1.5	—	84
40. Sodium Alkyl Sulfate, Principally Lauryl	0.5	1.5	—	53
41. Graphite Powder	15	1.5	None	None
42. $Al(OH)_3$ Powder	15	1.5	89	92
43. Salicylic Acid	15	1.5	63	—
44. Nicotinyl Salicylic Acid	15	1.5	41	26
45. 1 (+) Histidine HCl	15	1.5	None	—
46. 1 (+) Tyrosine	15	1.5	None	None
47. 9-Aminoacridine HCl	15	1.5	None	—
48. Gentian Violet	15	1.5	81	—
49. Oil Black (Dye)	15	1.5	None	None
50. (Bentonite (Insoluble Polyamine (Resin A	5 5	1.5	72	72
51. Bentonite (Insoluble Polyamine (Resin A	7.5 7.5	1.5	93	93

TABLE II

	Substance Tested	Concentration mg/5 cc.	Conc. 1:3000 N. F. Pepsin mg/5 cc.	% Inhibition (Heterogeneous Mixture)	% Inhibition (Supernatant Liquid)
52.	Bentonite (Insoluble Polyamine (Resin A	5 10	1.5	88	100
53.	(Bentonite (Sodium Alkyl Sulfate	7.5 7.5	1.5	100	100
54.	(Bentonite (Synthetic NaAl (Silicate	7.5 7.5	1.5	97	97
55.	(Insoluble Polyamine (Resin (Sodium Alkyl Sulfate	14.5 0.5	1.5	94	100
56.	(Insoluble Polyamine (Resin (Sodium Alkyl Sulfate	14 1	1.5	99	100
57.	(Insoluble Polyamine (Resin (Sodium Alkyl Sulfate	13 2	1.5	100	100
58.	(Insoluble Polyamine (Resin (Sodium Alkyl Sulfate	10 5	1.5	100	100

CONCLUSION

The specific inhibitory power of an insoluble polyamine resin was enhanced by the addition of small amounts of sodium alkyl sulfate, principally lauryl; as low as one part of the sodium alkyl sulfate in thirty of the resin was effective. The mechanism of this combined reaction has not been fully evaluated, although it has been previously stated (34) that sodium lauryl sulfate acting independently has a protein denaturing action. Peptic activity has been inhibited by many diverse agents and various mechanisms of action have been advanced to explain this. Charcoal (16), alumina (38), $Ca_3(PO_4)_2$ (18), proteins (22), proteoses (8), etc., have been shown to adsorb pepsin; colloidal $Al(OH)_3$ to precipitate it with an excess of acid again liberating the enzyme (39), and others (13) have shown it to be destroyed by alkali at a pH 6.

The addition of the sodium alkyl sulfate to the polyamine resin not only increased the specific inhibitory power of the resin for pepsin, but also increased the speed of action with which this took place; the rate of speed with which acid was neutralized by the resin was increased and pepsin inactivation aided.

In the series of agents tested as pepsin inhibitors in this study, three or more mechanisms are operative. In the instance of activated charcoal, surface adsorption is the basis. In the case of protein hydrolysate, the mass action effect of end products is probably operative. With gentian violet, chemical interaction with complex formation is most logical hypothesis. Beyond question however, many other foundations of antipeptic activity exist and any one or combination of these may be responsible in a specific instance of enzymatic inhibition.

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NUTRITION

Vitamins and Hormones in Nutrition. V: Emotional Upset and Trauma

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THE PRESENT COMMUNICATION completes a series of five reports in which a number of etiologic entities in nutritional disturbances have been discussed. The first report (1) was devoted to the synergistic action of vitamins and hormones and the etiological factors involved in 200 cases of nutritional disorders. Detailed anaylsis of each factor was presented in the remaining publications in the series. Thus, the effect of hormone dyscrasia on vitamin absorption was described in the second paper (2). The third (3) demonstrated the role of infection in nutritional disturbances. The importance of food intake and the interference with food absorption as related to nutritional balance was discussed in the fourth paper (4). This, the fifth and concluding report in the series, will present in detail the significance of both emotional upset and trauma as etiological factors in nutritional disorders. In 50 cases or 25 per cent of the 200 cases emotional upset was either the primary or a contributing factor; and in only 15 cases or eight per cent did trauma enter the disturbed nutritional picture.

The importance of "emotional upsets" in numerous symptom-complexes is indicated in the voluminous literature which has appeared on this subject during the last ten years. Different terms are used to label these psychic disturbances such as anxiety state, neurosis, psychoneurosis, and psychosomatic disease. But the author prefers to call it "the emotional state." It has been asserted that no anatomical system or physiological function is immune from a psychosomatic upset, and in these patients, thoughts and emotions can conjure or initiate symptoms comparable to those encountered in disease. For example, complexes simulating cancer, with associated weight loss, weakness, anorexia, diarrhea, anemia, and actual pain, are not uncommon. There is no question that cell metabolism is altered in these emotional upsets. We have all seen marked physical changes occur in individuals who have had their peace of mind seriously disturbed, as for instance by financial reverses, a broken love affair, or the sudden death of a relative or close friend. In extreme cases prolonged emotional upset may cause loss of appetite, diminished food intake, and loss in weight. This results in improper vitamin absorption

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Submitted July 14, 1948.