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Autonomic Drug Effects and Gastric Secretion in a New Experimental Model of Stress Ulcers in Rats

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MINE, K., T. NODA, M. FUJIWARA, N. TSURUTA, S. UEKI AND T. NAKAGAWA. *Autonomic drug effects and gastric secretion in a new experimental model of stress ulcers in rats.* PHARMACOL BIOCHEM BEHAV **19**(2) 359–364, 1983.—A psychological procedure which does not involve the application of physical stimulation was used to produce gastric ulcers experimentally. Ulceration was induced in rats by exposing the animals to the aggressive attacks of rats treated with 6-hydroxy-dopamine (6-OHDA). Gastric secretion and the effects of autonomic drugs on ulcer formation were investigated. Atropine methylbromide did not significantly inhibit the occurrence of erosions. Phentolamine or hexamethonium bromide significantly inhibited the production of erosions, and combined administration of an anticholinergic agent and α-blocking agent led to a complete inhibition, with no notable behavioral change. In case of pylorus ligation, gastric secretion during exposure to attack of 6-OHDA-treated rats was significantly less than that in the controls. We suggest that the sympathetic nervous system plays an important role in the production of gastric erosions, as induced by the methods reported in this study.

Aggressive behavior Stress ulcers Gastric secretion Adrenergic blockers Ganglion blockers Anticholinergic drugs

PREVIOUS experimental models of stress ulcers have used forms of physical stimulation such as restraint, cold and electric shock as stressor while concurrently starving the animals [1, 9, 12, 31]. These techniques have produced considerable information regarding the etiology and pathogenesis of peptic ulcer disease [1,12].

However difficulties exist when we attempt to draw conclusions on psychological or physiological mechanisms related to human peptic ulcer disease, from the results obtained by these experimental models employing physical stress.

The association between human peptic ulcer disease and gastrointestinal pathology in animal models is a difficult one to establish due to extreme differences in situations in which ulcer is elicited. Mikhail [31] concluded that in the literature on experimental ulcer, there had been no convincing demonstrations indicating that psychological factors induce ulcers, and that food deprivation or physical stimulation used in experimental procedures would mainly contribute to the occurrence of gastric pathology.

In the occurrence and the course of human peptic ulcer, social or emotional factors are thought to be important [2,44] as well as genetic factors and others [38,44].

We reported a new experimental model of stress ulcers, and suggested that the non-physical, psychological factors play an important role in the production of gastric erosion in this model [32].

When rats treated with 6-hydroxydopamine (6-OHDA), housed in isolation, and subjected to continuous tail pinching were paired with untreated rats, violent fighting behavior occurred, establishing a dominant-subordinate relationship in which the untreated rats consistently played the subordinate role.

Following one hour of paired housing, a high incidence of gastric erosion associated with marked bleeding occurred in the untreated rats. Untreated rats attacked during the one hour of paired housing received few serious body wounds and there was no difference in the erosion incidence between rats sustaining bite wounds and these that did not.

In studies by Desiderato *et al.* who used shock stress, significant ulcer was not found unless animals experienced a minimum of 2 hr post-stress rest prior to sacrifice. They suggested a strong parasympathetic rebound would contribute to ulcer formation [9]. With our method, erosion could be produced at a high incidence, even in the absence of the post-stress rest.

Thus, we speculated that pathophysiological mechanisms eliciting gastric lesion in our model differed from mechanisms in previous models using physical stress.

The autonomic nervous system is thought to paly an important role in the pathogenesis of peptic ulcer disease, however, the mechanism by which this system is involved in the production of peptic ulcer in humans remains a question [6,23].

The present experiment was carried out under the assumption that our new experimental model would provide

pertinant informations concerning the etiology and pathogenesis of peptic ulcer disease.

We attempted to clarify the role of the autonomic nervous system in the occurrence of gastric erosion by investigating the effect of autonomic drugs on the occurrence of erosion, and by examining gastric secretion in stressed rats in our model.

METHOD

Eighty male Wistar rats weighing 200–250 g obtained from the Kyushu Institute of Experimental Animals were intraventricularly given 500 μg of 6-OHDA by the method we have already reported [32].

Following four weeks of isolated housing, responsiveness to tapping, handling and pinching was scored [34] and sixty rats exhibiting a score of at least 10 of the maximal number of 12 points were selected, further subjected to isolated housing for one to five weeks and used in the fighting behavior experiments.

The body weight of the animals was 320–420 g at the time of these experiments. Animals subjected to attack by 6-OHDA-treated rats included one hundred and fifty two male Sprague-Dawley (SD) rats weighing 200–250 g raised in group housing in the Animal Center of Kyushu University. After drug injection, or pylorusocclusion, SD rats were individually placed in the home cage of each 6-OHDA-treated rat. At the commencement of paired housing, the tail of the 6-OHDA-treated rat was continuously pinched with a metal clip. During this period free access was allowed to food and water. The fighting behavior between the two species was observed for 1 or 2 hr. The fighting posture of the two models was recorded at 5-min intervals commencing 5 min after the start of paired housing, a total of 12 times for 1 hr or 24 times for 2 hr, according to the definitions of Grand [13], Miczek [29], and Carlini [7]. For each rat, the number of agressive postures was recorded as the dominant score and the total number of defensive upright, immobile crouch and submissive supine posture was recorded as the subordinate score. The number of body wounds with the length of 1 mm sustained by SD rat as a result of biting by the 6-OHDA-treated rat was also recorded. Any SD rat with a subordinate score of $\leqq 8$ in fighting for 1 hr or of $\leqq 16$ in fighting for 2 hr was excluded from the experiment. 6-OHDA-treated rats were used a maximum of three times each. Testing on consecutive days was avoided.

Fighting between rats housed in pairs was consistently investigated from the hour of 1500. Throughout the study, the room was maintained at a temperature of 23 ± 1°C.

Illumination was provided on a 12-hr light-dark cycle with lights on from 0700 hr to 1900 hr. For group housing, plastic cages measuring $30 \times 25 \times 17$ cm were used. 6-OHDA-treated rats were housed individually in metal wire mesh cages measuring $18 \times 17 \times 17$ cm.

Autonomic Drugs and Examination of the Gastrointestinal Tract

The effects of autonomic drugs on the production of gastric erosion induced by the fighting behavior were investigated.

One hundred and twenty-four male SD rats weighing 200–250 g were used. Food and water were supplied ad lib. Sixty-four rats were randomly grouped into eight respectively consisting of eight rats. Six groups were given intraperitoneally one drug and 0.9% saline. Drugs given were: atropine methylbromide at 10 and 20 mg/kg, phentolamine at 5, 10 and 20 mg/kg and phenoxybenzamine at 10 mg/kg. Two groups were given intraperitoneally an anticholinergic agent, 10 mg/kg of atropine methylbromide, concomitantly with an α-blocking agent, 10 mg/kg of phentolamine or 20 mg/kg of phenoxybenzamine. As a control, sixteen rats were injected with 0.9% saline in two administrations and by the same route.

Sixteen rats were randomly and equally grouped, and the two groups were given intraperitoneally hexamethonium bromide at 40 mg/kg or 60 mg/kg. As a control, twelve rats were injected with 0.9% saline by the same route. Drugs were dispersed in 0.9% saline.

Thirty minutes after these treatments, rats were individually placed in the same home cage of each 6-OHDA-treated rat. After 1 hr of fighting behavior, these rats were returned to their home cage and the gastrointestinal tract was observed after 1 hr, in the same manner as reported previously [32].

The incidence and the severity of gastric erosion were assessed. The severity of the erosions was rated on a 4-point scale as follows: 0=no visible erosion or blood; 1=one or several small clearly visible erosions; 2=one or several intermediate erosions with moderate bleeding; 3=one or several large erosions and marked bleeding, even to the small intestine.

Collection and Analysis of Gastric Contents

Fourteen male SD rats weighing 200 to 220 g were prepared for pyloric occlusion by the method reported by Dai and Ogle [8], and were used on the 8th post-operative day when the body weight had reverted to the pre-operative level. A stainless steel wire loop was placed around the pylorus in each rat, and from the 6th day after this treatment all food and water was withheld for 48 hr, except for free access to 8% sucrose in 0.2% NaCl which was removed 1 hr before the experiment. The collection of gastric juice was begun by pulling on the two externally exposed sections of the wire led out at the flanks.

In eight, pyloric ligation was performed immediately before the fighting behavior experiment. The fighting behavior between the two rats was observed for two hours thereafter.

The other six rats were returned to their home cage immediately after the pyloric ligation and served as the control group. Two hours after the pyloric ligation, all the rats were immediately anesthetized with ether.

After clamping the cardia, the stomachs were removed and the gastric contents were collected in a graduated centrifuge tube through the punctured fundus. After centrifugation at 3500 rpm for 15 minutes, the total acidity of the supernatant was determined by titration with 0.01 N NaOH to an end point of pH 7.0, using an electronic pH meter. The pepsin activity was determined by measuring the quantity of tyrosine liberated by the proteolytic digestion of hemoglobin by the gastric juice [11].

Chi-square test was used to determine the statistical significance in the incidence of gastric erosion. Gastric secretion and the severity score of erosions were analyzed by means of Student's t-test.

RESULTS

Effects of Autonomic Drugs on the Occurrence of Gastric Erosion

As in our previous work [32], immediately after the com-

TABLE 1

THE INCIDENCE AND THE SEVERITY SCORES OF GASTRIC EROSION AND DOMINANT SCORES, SUBORDINATE SCORES AND NUMBER OF BODY WOUNDS IN RATS GIVEN ATROPINE METHYLBROMIDE AND α-BLOCKING AGENT SINGULARLY OR IN COMBINATION

Treatment	Dose (mg/kg)	No. of rats	Incidence of erosions (%)	Severity score of erosions (±S.E.)	Behavioral score		
					Dominant score (±S.E.)	Subordinate score (±S.E.)	No. of wounds (±S.E.)
0.9% saline		16	81	1.6 ± 0.3	0	11.2 ± 0.1	2.0 ± 0.4
Atropine methylbromide	10	8	75	1.5 ± 0.4	0	11.9 ± 0.1	1.5 ± 0.4
	20	7	43	0.7 ± 0.3	0	11.3 ± 0.4	1.1 ± 0.7
Phentolamine	5	8	50	1.1 ± 0.5	0	11.8 ± 0.1	1.1 ± 0.5
	10	8	38	0.5 ± 0.3*	0	12.0 ± 0	0.9 ± 0.4
	20	8	75	1.8 ± 0.4	0	11.8 ± 0.1	1.8 ± 0.8
Phentolamine + Atropine methylbromide	20 10	8	0†	0†	0	12.0 ± 0	2.0 ± 1.4
Phenoxybenzamine	10	8	75	1.5 ± 1.1	0	12.0 ± 0	3.6 ± 1.2
Phenoxybenzamine + Atropine methylbromide	10 10	8	0†	0†	0.5 ± 0.5	11.4 ± 0.5	2.1 ± 2.0

*Significantly different from control ($p<0.02$).
†Significantly different from control ($p<0.001$).

mencement of paired housing all the 6-OHDA-treated rat began to explosively attack the SD rat and fighting started.

After several minutes all 6-OHDA-treated rats assumed an aggressive posture while chattering their teeth and hissing.

Most of the SD rats given saline or drug injections assumed a defensive upright posture or a submissive supine posture while squealing. Thereafter the dominant-subordinate relation between the paired rats was consistently maintained for 1 hr. Only one rat given 20 mg/kg of atropine methylbromide showed a subordinate score of ≦8 and was therefore excluded from the results.

In the behavioral observation, the subordinate score and the number of body wounds of the rats given autonomic drugs were not significantly different from those of control, except that some rats given 40 mg/kg of hexamethonium bromide or 10 mg/kg of phenoxybenzamine and 10 mg/kg of atropine methylbromide in combination exhibited an agressive posture for a short time.

Gastric erosion accompanied by marked bleeding was observed in a high incidence (81%) in the control group as seen in previous work [32].

Effect of Atropine Methylbromide

In contrast with previous reports on restraint ulcer [3, 12, 17, 26, 31, 37, 42], atropine methylbromide did not significantly inhibit the occurrence of gastric erosion, though a large dose (20 mg/kg) of atropine methylbromide tended to inhibit the severity of erosion ($t=1.91$, $p<0.10$) (Table 1).

Effect of α-Blocking Agents

The single administration of 10 mg/kg of phentolamine significantly inhibited the occurrence of erosion in severity ($t=2.61$, $p<0.02$) and tended to inhibit in incidence ($\chi^2=2.84$, $p<0.10$) but with no significant behavioral change.

This inhibitory effect was not augmented by increasing the dose. Ten mg/kg of phenoxybenzamine had no inhibitory effect (Table 1).

Effect of a Combination of α-Blocking Agent and Atropine Methylbromide

Single administration of 20 mg/kg of phentolamine or 10 mg/kg of phenoxybenzamine had no inhibitory effect on the occurrence of gastric erosion.

However it is of interest that the combined administration of atropine methylbromide and the increasing dose of α-blocking agent completely inhibited the occurrence of erosion with no difference in subordinate score and body wounds, in comparison with control (Table 1).

Effect of Hexamethonium Bromide

The occurrence of erosion was not attenuated by 40 mg/kg of hexamethonium. While increasing dosage of the drug (60 mg/kg) markedly suppressed the incidence and the severity of erosions, ($\chi^2=4.59$, $p<0.05$ and $t=2.95$, $p<0.01$, respectively).

There were no notable effects of the drug on subordinate score and body wounds (Table 2).

Gastric Secretion in Pylorus-Ligated Rat Under Attack Stress

As in our previous report [32] and the autonomic drugs experiment described above, fighting episodes were equally observed between 6-OHDA-treated and pylorus-ligated rats. Behavioral scores in pylorus-ligated rats were as follows: aggressive score 0±0, subordinate score 22.2±0.6, body wounds 3.1±0.6. No rat showed a subordinate score ≦16. As shown in Table 3, the secretory volume and total acid

TABLE 2

INCIDENCE AND SEVERITY SCORES OF GASTRIC EROSION AND DOMINANT SCORES, SUBORDINATE SCORES AND NUMBER OF BODY WOUNDS IN RATS GIVEN HEXAMETHONIUM BROMIDE

Treatment	No. of rats	Incidence of erosions (%)	Severity score of erosions (±S.E.)	Behavioral score: Dominant score (±S.E.)	Behavioral score: Subordinate score (±S.E.)	No. of wounds (±S.E.)
0.9% saline	12	83	1.7 ± 0.3	0	12 ± 0	2.2 ± 0.2
Hexamethonium bromide 40 mg	8	50	0.8 ± 0.3	0	12 ± 0	1.9 ± 0.6
60 mg	8	25*	0.4 ± 0.3†	0.3 ± 0.3	11.8 ± 0.3	0.9 ± 0.5

*Significantly different from control ($p<0.05$).
†Significantly different from control ($p<0.01$).

TABLE 3

EFFECT OF ATTACK BY 6-OHDA-TREATED RATS ON GASTRIC SECRETION IN PYLORUS-LIGATED RATS

Group	Number of rats	Body weight (g)	volume (ml/100 g of b.w./hr)	Acid output (μEq/hr)	Pepsin output (mg/hr)
Control	6	215 ± 4	0.75 ± 0.15	29.8 ± 0.7	1.54 ± 0.26
Stressed	8	211 ± 4	0.35 ± 0.03*	11.8 ± 1.4*	0.79 ± 0.10*

All values represent mean ± S.E.
*Significantly different from control ($p<0.02$).

output in the unstressed group (n=6) were 0.75 ml/100 g of body weight/hr, 29.8±0.7 μEq/hr and 1.54±0.26 mg/hr, respectively. However, secretory volume, acid output and pepsin output in pylorus-ligated rats attacked by the 6-OHDA-treated rats (n=8) were all significantly suppressed by about 50% or more, in comparison with the unstressed group, ($t=2.73, p<0.02$, $t=2.77, p<0.02$ and $t=2.72, p<0.02$, respectively).

DISCUSSION

The effects of autonomic drugs on the production of gastric lesions induced by a restraint technique in rats have been well investigated. Most workers concluded that small doses of anticholinergic agents significantly inhibited the occurrence of restraint ulcer [3, 12, 17, 26, 31, 37, 42].

With regard to the effect of α-adrenergic blocking agents on the production of restraint ulcer in rats, conflicting reports have appeared. Okabe *et al.* reported that phentolamine increased the severity of gastric erosions induced by restraint-immersion [36], and other studies showed that α-adrenergic blocking agents had no significant effect [37,41]. On the other hand, it was reported that the occurrence of gastric lesions was significantly inhibited by α-adrenergic blocking agents [3,26]. Djahanguiri *et al.* reported that the norepinephrine turnover rate was significantly increased in the glandular stomach of rats subjected to restraint and that phenoxybenzamine or phentolamine significantly reduced the incidence of cold-restraint induced gastric lesions [10].

Takagi and Okabe reported that under conditions of restraint-immersion stress, anticholinergic drugs completely inhibited the development of stress ulcer in rats, whereas a new type of ulcer could be induced by the administration of increasing doses of the drugs [40], and that phentolamine and tolazoline significantly decreased the production of the new type of ulcer [41].

The results of these studies indicate that the parasympathetic nervous system plays a predominantly important role in the production of restraint ulcer. However, it was also suggested that adrenergic factors may be involved in the production of gastric lesion. The gastric lesions in our new experimental model of stress ulcer were not inhibited by a single administration of anticholinergic agent, but were significantly inhibited in severity by a single administration of an α-adrenergic blocking agent, or a ganglion blocker yet there was no significant change in fighting behavior. Combined administration of an α-blocking agent and an anticholinergic agent completely inhibited the production of gastric erosions, in the absence of behavioral changes. With regard to the effect of restraint stress on gastric secretion in rats, the data previously reported ranged from a decreased [8, 9, 16, 28] to an increased influence [22]. In addition, Mikhail [30] found that chronic conditioned fear decreased gastric acidity in pylorus-ligated rats in contrast with an earlier report of Mahl [25] that chronic exposure to conditioned fear increased gastric acidity in dogs. Dai and Ogle [8] reported a new method of pylorus ligation, and concluded that, with this method regarded as less unphysiological than the Shay technique [39], gastric secretion was significantly higher than in the Shay technique.

Using their new method of pylorus ligation, gastric secretion in rats exposed to attack of 6-OHDA-treated rats was significantly lower than that in the controls. The role of the

sympathetic nervous system in controlling mechanisms related to gastric secretion is still not well understood. However previous reports have shown that the sympathetic nervous system has an inhibitory effect on gastric secretion. Grund *et al.* [14] and Blair *et al.* [5] reported that electrical stimulation of the splanchnic nerve significantly reduced the acid output in response to gastrin infusions, vagal stimulation or meat extracts in cats. Many authors found that surgical or chemical sympathectomy increased gastric secretion in experimental animals [19, 21, 24, 33, 35]. Vizi reported that in the entire gastro-intestinal tract, the sympathetic transmitter, noradrenaline, controlled the parasympathetic nerve-effector transmission by reducing the acetylcholine release presynaptically [43]. Thus, it is suggested that when gastric secretion is reduced, the sympathetic nervous system is predominantly activated. Though the involvement of the cholinergic system cannot be neglected, the sympathetic nervous system probably plays an important role in the production of gastric erosions in our method. We speculate that the sympathetic nervous system may be involved in the production of gastric erosions by reducing the mucosal blood flow in the stomach. Guth and Smith [15] and Kalahanis *et al.* [20] demonstrated direct adrenergic innervation of the gastric mucosal arteriorles. Moreover, it has been reported that stimulation of the sympathetic nerves to the stomach [5,14] or the administration of sympathetic substances [4,18] decreased the mucosal blood flow. Menguy and Masters found that gastric lesion was produced by mucosal ischemia following protracted hypotension, and that the production was prevented by an α-adrenergic blocking agent [27].

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REFERENCES

1. Ackerman, S. H. Restraint ulceration as an experimental disease model. *Psychosom Med* **37:** 4–7, 1975.
2. Alexander, F. *Psychosomatic Medicine* New York: W. W. Norton, 1950, pp. 101–115.
3. Beattie, D. Effect of drugs on rats exposed to cold-restraint stress. *J Pharm Pharmacol* **29:** 748–751, 1977.
4. Bhargava, K. P., M. B. Gupta and K. K. Tangri. Mechanism of ulcerogenic activity of indomethacin and oxyphenbutazone. *Eur J Pharmacol* **22:** 191–195, 1973.
5. Blair, E. L., E. R. Grund, J. D. Reed, D. J. Sanders, G. Sanger and B. Shaw. The effect of sympathetic nerve stimulation on serum gastrin, gastric acid secretion and mucosal blood flow responses to meat extract stimulation in anesthetized cats. *J Physiol* **253:** 493–504, 1975.
6. Brooks, F. P. and E. F. Rosato. The vagus nerves: their significance for gastrointestinal function and peptic ulcer disease. *Viewpoints Dig Dis* **6:** 4, 1974.
7. Carlini E. A. Further studies of the aggressive behavior induced by Δ^9-tetrahydrocannabinol in REM sleep-deprived rats. *Psychopharmacologia* **53:** 135–145, 1975.
8. Dai, S. and C. W. Ogle. A new method for the collection of gastric secretion in conscious rats. *Pflügers Arch* **336:** 111–120, 1972.
9. Desiderato, O., J. R. Mackinnon and H. Hissom. Development of gastric ulcers in rats following stress termination. *J Comp Physiol Psychol* **87:** 208–214, 1974.
10. Djahanguiri, B., H. L. Taubin and L. Landsberg. Increased sympathetic activity in the pathogenesis of restraint ulcer in rats. *J Pharmacol Exp Ther* **184:** 163–168, 1973.
11. Glass, G. B. J., B. L. Pugh, S. Wolf. A new modification of the hemoglobin technic for the determination of pepsin in gastric juice adapted for a wide range of values. *Rev Gastroenterol* **18:** 670–678, 1951.
12. Glavin, G. B. Restraint ulcer: History, current research and future implications. *Brain Res Bull* **5:** 51–58, 1980.
13. Grant, E. C. and J. H. Mackintosh. A comparison of the social postures of some common laboratory rodents. *Behavior* **21:** 246–259, 1963.
14. Grund, E. R., J. D. Reed and D. J. Sanders. The effect of sympathetic nerve stimulation on acid secretion, regional blood flows and oxygen usage by stomachs of anaesthetized cats. *J Physiol* **248:** 639–647, 1975.
15. Guth, P. H. and E. Smith. Neural control of gastric mucosal blood flow in the rat. *Gastroenterology* **69:** 935–940, 1975.
16. Hano, J., J. Bugajski, L. Danek and CZ. Wantuch. The effect of neuroleptics on the development of gastric ulcers in rats exposed to restraint-cold stress. *Pol J Pharmacol Pharm* **28:** 37–47, 1976.
17. Hanson, H. M. and D. A. Brodie. Use of the restrained rat technique for study of the antiulcer effect of drugs. *J Appl Physiol* **15:** 291–294, 1960.
18. Holton, P. Catecholamines and gastric secretion. In: *Pharmacology of Gastrointestinal Motility and Secretion.* Section 39, vol 1. Oxford: Pergamon Press, 1973, pp. 287–315.
19. Hottenrott, C., R. M. Seufert, F. Kühne and M. Büsing. Experimental gastric sympathectomy: An effective prophylaxis of gastric stress lesions. *Ann Surg* **186:** 762–765, 1977.
20. Kalahanis, N. G., T. K. Das Gupta, L. M. Nyhus. Neural control of blood flow in gastric mucosa. *Am J Surg* **131:** 86–90, 1976.
21. Kasuya, Y., T. Maruta and S. Okabe. Influence of surgical sympathectomy on gastric secretion and ulceration in rats. *Jpn J Pharmacol* **28:** 297–304, 1978.
22. Kitagawa, H., M. Fujiwara and Y. Osumi. Effects of water-immersion stress on gastric secretion and mucosal blood flow in rats. *Gastroenterology* **77:** 298–302, 1979.
23. Kraft, R. O., J. Myers, S. Overton and W. J. Fry. Vagotomy and the gastric ulcer. *Am J Surg* **121:** 122–126, 1971.
24. Lillehei, C. and O. H. Wangensteen. Effect of celiac ganglionectomy upon experimental peptic ulcer formation. *Proc Soc Exp Biol Med* **68:** 369–372, 1948.
25. Mahl, G. F. The effect of chronic fear on the gastric secretion of HCl in dogs. *Psychosom Med* **11:** 30–44, 1949.
26. Manekar, M. S. Effect of autonomic drugs on the stress induced acute gastric ulceration in rat. *Indian J Physiol Pharmacol* **20:** 160–163, 1976.
27. Menguy, R. and Y. F. Masters. Mechanism of stress ulcer—Influence of α-adrenergic blockade on stress ulceration and gastric mucosal energy metabolism. *Dig Dis* **23:** 493–497, 1978.
28. Menguy, R. Effects of restraint stress on gastric secretion in the rat. *Am J Dig Dis* **5:** 911–916, 1960.
29. Miczek, K. A. Intraspecies agression in rats: Effects of d-amphetamine and chlordiazepoxide. *Psychopharmacologia* **39:** 275–301, 1974.
30. Mikhail A. A. Effects of acute and chronic stress situations on stomach acidity in rats. *J Comp Physiol Psychol* **74:** 23–27, 1971.
31. Mikhail A. A. Psychological stress and stomach ulcer: In search of an hypothesis. *Brain Res Bull* **5:** 67–71, 1980.
32. Mine, K., T. Nakagawa, M. Fujiwara, Y. Ito, Y. Kataoka, S. Watanabe and S. Ueki. A new experimental model of stress ulcers employing aggressive behavior in 6-OHDA-treated rats. *Physiol Behav* **27:** 715–721, 1981.
33. Moraes M. F., L. M. Nyhus, N. G. Kalahanis, C. T. Bombeck and T. K. Das Gupta. Role of the sympathetic nervous system in peptic ulcer production in rats. *Surgery* **83:**194–199, 1978.

34. Nurimoto, S., N. Ogawa and S. Ueki. Hyperemotionality induced by lesions in the olfactory system of the rat. *Jpn J Pharmacol* **24:** 175–184, 1974.
35. Oberhelman, H. A., E. R. Woodward, C. A. Smith and L. R. Dragstedt. Effect of sympathectomy on gastric secretion in total pouch dogs. *Am J Physiol* **166:** 679–685, 1951.
36. Okabe, S., R. Saziki and K. Takagi. Effect of adrenergic blocking agents on gastric secretion and stress-induced gastric ulcer in rats. *Jpn J Pharmacol* **20:** 10–15, 1970.
37. Rosoff, C. B. and H. Goldman. Effect of the intestinal bacterial flora on acute gastric stress ulceration. *Gastroenterology* **55:** 212–222, 1968.
38. Rotter, J. I. and D. L. Rimoin. Peptic ulcer disease—A heterogeneous group of disorders? *Gastroenterology* **73:** 604–607, 1977.
39. Shay, H., S. A. Komarov, S. S. Fels, D. Meranze, M. Gruenstein and H. Siplet. A simple method for the uniform production of gastric ulceration in the rat. *Gastroenterology* **5:** 43–61, 1945.
40. Takagi, K. and S. Okabe. An experimental gastric ulcer of the rat produced with anticholinergic drugs under stress. *Eur J Pharmacol* **5:** 263–271, 1969.
41. Takagi, K. and S. Okabe. Studies of the mechanisms involved in the production of stress and stress-atropine ulcers in rats. *Eur J Pharmacol* **10:** 378–384, 1970.
42. Takagi, K., Y. Kasuya and K. Watanabe. Studies on the drugs for peptic ulcer. A reliable method for producing stress ulcer in rats. *Chem Pharm Bull (Tokyo)* **12:** 465–472, 1964.
43. Vizi, E. S. Interaction between adrenergic and cholinergic systems: Presynaptic inhibitory effect of noradrenaline on acetylcholine release. *J Neural Tansm Suppl* **11:** 61–78, 1974.
44. Weiner, H. *Psychology and Human Disease*. New York: Elsevier, 1977, pp. 29–101.