MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

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MEDICAL TREATMENT OF DUODENAL ULCER

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A. Diet
B. Smoking
C. Sedatives
D. Anticholinergics
E. Antacids
F. Radiation
G. Suggested Medical Therapy

A. Diet Therapy

1. History

The dietary history of peptic ulcer has been reviewed by Lawrence.[1] Up to the beginning of this century, Lenke's starvation regimen was the customary treatment. In 1901 Lenhartz reported to the Congress of Internal Medicine at Wiesbaden that small frequent feedings prevented recurrent bleeding in patients with presumed peptic ulcer. When it became possible to diagnose ulcer by x-ray, the Lenhartz diet was applied to patients even without hemorrhage. The diet was subsequently modified by Sippy, Hurst, and many others.

Serious efforts were never made by any of these workers to assess the therapeutic values of these methods, but the ulcer diet nevertheless became routine.

2. Milk

In 1940 Kirsner and Palmer[2] reported a study, primarily concerned with milk and cream and antacid regimens. In their Figure 1, they compared the effect of a 3-meal general diet in 17 experiments with 90 cc. of milk and cream hourly. pH values indicated more acid with the milk and cream regimen than with the 3-meal diet. It is curious that Kirsner in 1959 still recommended hourly milk-cream for treatment of peptic ulcer.[3]

Bingle and Lennard-Jones[4] compared a bland gastric diet with between-meal feedings with hourly drinks of 120 ml. of a mixture of 3 parts milk and 1 part cream. Patients had more acid more of the time with the milk treatment than with the bland diet.

There are no controlled studies showing that milk is beneficial in any form or at any stage of ulcer.

3. Bland Diet

a. Effect on gastric acidity:

Lennard-Jones and Babouris[6] have recently compared two bland ulcer diets with a general hospital diet in patients with duodenal ulcer. No differences were apparent.

b. Effect on clinical course:

Three controlled clinical trials of diet in the treatment of duodenal ulcer have been performed:

1) Lawrence[1] compared the Lenhartz diet with an ordinary hospital diet in 140 patients, alternating those that went into the control and treatment groups. Each got an antacid every 2 hours. Healing, as judged by x-ray and complete relief of pain, was slightly better in the patients who got the ordinary hospital diet.
2) Doll[5]: Controlled study, 64 patients with gastric ulcer, 80 outpatients with gastric ulcer and 50 outpatients with duodenal ulcer. Patients did slightly better on regular food than on bland diet.
3) Truelove:[7] In a well controlled 6-month study, patients on a "gastric diet" did no better than those on a freely chosen diet.

4. Gastric Secretory Response to Different Foods

Saint Hilaire, et al.[8] have reported the gastric secretory response of a stomach pouch (innervated) to a number of different foods in the dog. One hundred calories of each food in 250 ml. of water was studied. With beef given an arbitrary value of 100, they found:

Food	Relative Acid Secretion in Pouch
Beef	100
Haddock	214
Chicken	118
Eggs	71
Milk	70
Oatmeal	48
Wheaties	38
Peaches	17

Other foods were also studied.

A close correlation was found ($r = 0.97$) between the number of grams of protein per calorie in each food and the acid secreted in response to each calorie of the food. Furthermore, a close correlation was found between the buffering capacity of 100 calories of each food and the acid secretory equivalent of the food ($r = 0.81$).

Therefore, if man is like the dog, all foods should induce about the same amount of acid to accumulate in the stomach and to be emptied into the duodenum.

Caffeine and alcohol are exceptions.

Conclusions:

1) Caffeine and alcohol are the only substances which an ulcer patient should avoid.

2) There is no evidence that any dietary program reduces gastric acidity or peptic activity, promotes healing, or prevents recurrences of peptic ulcer.

3) Ulcer diets should not be prescribed, especially to an outpatient, because their inconvenience may make patients disregard all suggested therapy.

4) Milk should not be used therapeutically.

5) Multiple small feedings are of no benefit.

In spite of this evidence, tradition is difficult to break, i.e., Bockus, 1963: "The ideal food for the fulfillment of the criteria for dietary management of ulcer is milk."[9]

References:

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8. Saint Hilaire, S., et al. Stimulating effects of various foods in gastric acid secretion. Gastroenterology 9:1, 1960.

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B. Smoking

Nicotine renders ganglion cells at first more sensitive and then more resistant to acetylcholine; there is, therefore, a transient stimulation followed by a more persistent depression of autonomic ganglia.

1. Effect on Acid Secretion and Gastric Motility

It is not surprising that smoking, which admittedly involves more than nicotine, produces a variable effect on gastric acid secretion. Although some workers have found an increase in gastric secretion after smoking, most workers have found no change.[10] There is disagreement also on the effect of smoking on gastric contractions—some patients show increased contractions, some decreased, and some no change. Most workers have found that smoking does not affect gastric emptying.[10]

2. Effect on Symptoms of Peptic Ulcer

Most opinions in the literature are based on impressions unsupported by controlled (or other) study.

a. Jamieson, et al.[11] studied 473 ulcer patients and found that a change in smoking habits did not influence the severity of symptoms, i.e., changes in the amount of tobacco smoked after treatment for perforated peptic ulcer were unrelated to the severity of subsequent symptoms.

b. Doll, et al.[12]: 338 patients with duodenal ulcer and 2 matched controls for each. Heavy smokers did not have a higher incidence of ulcer, but a slightly higher percentage of ulcer patients smoked than the control patients.

c. The effect of smoking on healing of gastric ulcer in hospitalized patients receiving a variety of medical programs was studied in a poorly designed experiment by Doll, et al.[12] Patients who continued to smoke healed at the same rates as those who had never smoked. However, in patients who had previously smoked, and stopped, healing was somewhat more rapid by x-ray. The effect on the patients' symptoms was as follows:

	Number	Symptom-Free Throughout	Occasional Pain	Daily Pain For a Week or More
Advised to Stop	40	13	20	7
Not Advised to Stop	40	18	15	7

No similar studies are available for duodenal ulcer.

Conclusions:

There have been no good studies on the effect of smoking on the natural history of duodenal ulcer. What data are available suggest that smoking is not harmful.

References:

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11. Jamieson, R. A., Illingworth, C.F.W., and Scott, L.D.W. Tobacco and ulcer dyspepsia. Brit. Med. J. 2:287, 1946.

12. Doll, R., Avery Jones, F., and Pygott, F. Effect of smoking on the production and maintenance of gastric and duodenal ulcers. Lancet 1:657, 1958.

C. Sedatives

According to Avery Jones,[13] "The most important single drug in the management of peptic ulcer is phenobarbitone, given in sufficient doses to have the desired effect of sedation."

However, Truelove,[14] in a controlled study, found absolutely no benefit of phenobarbitone. The drug was randomly assigned, and this study strongly suggests that routine use of barbiturates is of no benefit. In selected cases, however, sedation might be of value, although there are no studies to prove the point. The same is true for tranquilizers.

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D. Anticholinergics

Bachrach critically reviewed the anticholinergic drug literature through 1958,[15] and concluded that these agents:

a. Inhibit basal secretion if given in doses which are near the limits of tolerance for the individual. This dose varies widely but is usually from 3 to 10 times the usual recommended dose. The effect lasts about 4 hours, but total output overnight is reduced by taking these agents at bedtime. For instance:

10-hour nocturnal period, mean for 8 patients on control nights and after 2 mg. glycopyrollate:

	Total Volume	mEq. Free Acid Collected
Control	636	18.1
Glycopyrollate	244	3.9

—From Barman and Larson, A. J. Med. Sci. p. 327, Sept. 1963

b. Have no consistent effect on the gastric secretory response to a meal, even when given in large doses.

c. Do not improve the results of treatment in uncomplicated duodenal ulcer, nor do they prevent recurrences.

d. Prolonged action forms of anticholinergic agents do not, in fact, have prolonged action.

e. One anticholinergic agent is as good as another.

f. Beware prostatic hypertrophy and elderly patients. Contraindicated in peptic esophagitis.

Since 1958, several papers are noteworthy:

1. Effect of anticholinergics on meal-induced gastric secretion:

a. Bingle, et al.[16], Lennard-Jones,[17] and Soergel and Hogan[18] showed that Poldine and Robinul in optimum doses did not reduce acidity of the gastric contents of patients taking a bland diet with in-between feedings or antacids.

b. Mitchell, et al. (Poldine)[19] and Collyns, et al. (Robinul)[20] showed that in effective doses anticholinergics depress gastric acidity after a single meal without antacids. Collyns found no depression of peptic activity in the same studies.

c. Robinul in optimum therapeutic doses did not potentiate a single 8 gm. dose of calcium carbonate given one hour after a meal.[21]

2. Effect on the disease - Controlled studies:

a. Lennard-Jones[17]: 11 patients. 3 months on placebo and 3 months on Poldine in optimum doses. Exacerbations occurred with equal frequency.

b. Melrose and Pinkerton[22]: "Double blind" study:

	Number of Patients	Number of Exacerbations	Period of Observation
Poldine	31	15	290 months
Placebo	37	11	219 months

c. Sun[23]: 18-month study:

	Number of Patients	% Developing Recurrence
Robinul	20	15
Placebo	17	71

This is the only controlled study of many in which anticholinergics were found to favorably alter the course of duodenal ulcer. Sun believes beneficial effects were noted because of careful titration of dose. (How a study can be double-blind under these circumstances is difficult to understand.) For negative studies, see Bachrach.[15] If anticholinergics favorably influence the couse, it may well be due to the bedtime dose, and not the anticholinergic medication during the day.

Conclusions:

1) Anticholinergic drugs are effective in reducing basal and nocturnal secretion of acid if given in a dose that causes slight side-effects.

2) Recent studies suggest that optimum doses of anticholinergics reduce gastric secretion in response to a single meal, but not when patients are on a bland diet with multiple feedings or on an hourly antacid program.

3) Anticholinergics do not potentiate the effect of a single dose of antacid given one hour after a meal.

4) Only one of many studies suggests that anticholinergic drugs favorably influence the course of duodenal ulcer, but this one study may possibly be the most carefully done. However, its author is a long-time enthusiast of anticholinergic therapy. The major advantage is probably the nocturnal dose.

5) May be useful in "pylorospasm", but no proof of this.

6) Serious side-effects high in elderly and debilitated patients.

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E. Antacids

1. Chemical Reactions Leading to Neutralization of Gastric Acidity

a. Calcium Carbonate:

$$CaCO_3 + 2\ HCl \longrightarrow CaCl_2 + H_2O + CO_2$$

In the small intestine, the calcium chloride is converted to poorly soluble calcium salts and the chloride is reabsorbed. Since the unneutralized calcium carbonate is relatively insoluble, there is little effect on acid-base balance (see Milk Alkali Syndrome below).

b. Aluminum Hydroxide:

$$Al(OH)_3 + 3\ HCl \longrightarrow AlCl_3 + 3\ H_2O$$

In the small intestine, the $AlCl_3$ reacts with small bowel fluids to form insoluble basic aluminum salts. No effect on acid-base balance.

2. What Constitutes Adequate Neutralization? No one knows.

3. Value of Antacids in Treatment of Ulcer is Controversial

a. Grossman, 1962:[24] "The keystone of medical treatment of duodenal ulcer is antacid therapy."

b. Sun, 1962:[25] "The common practice of taking antacid 3 times a day after meals is inadequate therapy as it probably does not prolong the neutralizing effect of the meal itself."

c. E. Palmer, 1962:[26] "I just want to say that we haven't used an antacid in our clinic for the last 15 years."

4. Relative Effectiveness of Antacids[27]

	In Vitro Neutralizing Capacity (to pH 4.5 at 10 minutes) of 1 gm. active ingredient: ml 0.1 N HCl	Estimated Hourly Dose Required to Neutralize 50 mEq. HCl in 90% of Male Duodenal Ulcer Patients
Na_2CO_3	167	—
$NaHCO_3$	115	4.4 gm.
$CaCO_3$	110	4.5 gm.
MgO	87	5.9 gm.
$Al(OH)_3$ gel	12	715 ml.
Mg trisilicate	10	50.0 gm.
$MgCO_3$	7	63.0 gm.
$BiCO_3$	5	—

Liquids are far more effective than tablets, because mixing is better. In addition, Piper estimates than 20 ml. of liquid Titralac is equal to 18 tablets in vitro.

5. Economic Considerations

The high cost of antacid therapy has been discussed by Brody, et al.[28] Calcium carbonate preparations are the least expensive.

6. Acid Rebound

In the past it has been commonly stated that ingestion of alkali produces a secondary gastric response, supposedly via gastrin release, with rebound hyperacidity. In an extensive and critical review, Perira-Lima and Hollander concluded that there is no good evidence for acid rebound.[29] These workers also presented experiments in dogs with denervated pouches, and could not demonstrate acid rebound.[30]

7. Principles of Antacid Therapy

a. Basal state

1) Duration of action: 20-40 minutes[24]
2) To be effective, antacids have to be given at least hourly[24, 27]
3) Doubling the dose of an antacid does not prolong the neutralization[31]

b. In patients who eat (The following is taken from unpublished data, obtained with Dr. Adrian Collyns. No similar data are available in the literature):

1) 4 gm. $CaCO_3$ given one hour after eating reduces C_{H^+} (H^+ concentration) for 4 hours after the meal. See Figure 2.

2) By contrast, when given 4 hours after eating, 4 gm. $CaCO_3$ depresses C_{H^+} for only one hour. See Figure 4.

3) 8 gm. $CaCO_3$ has a longer and more potent effect than 4 gm., and depresses C_{H^+} for 5 hours. See Figure 3.

4) Optimum therapeutic dose of anticholinergic does not potentiate the effect of one dose of antacid given one hour after a meal.

5) 4 gm. $CaCO_3$ reduces C_{H^+} to a greater extent than 15 ml. Maalox.

6) Postcibal peptic activity is reduced by 4 gm. $CaCO_3$ but not by 15 ml. of Maalox.

8. Clinical Results

Apparently, controlled studies on the effectiveness of antacids in preventing ulcer recurrence have not been carried out.

9. Milk Alkali Syndrome[32-40]

Case Report:

[redacted], a 56-year-old [redacted] male executive from Dallas, first came to our attention in [redacted] 1965 with a history of having had ulcer-type abdominal discomfort for some 30 years. His pain had always been relieved by food and/or antacids until the past two years, during which time he had begun to receive less and less relief by these measures. At that time he had scarring of the duodenal bulb without actual ulceration being demonstrated. Hemoglobin was normal. There was no history of bleeding.

Calcium carbonate was prescribed, 4 gm. one and three hours p.c. and h.s., plus anticholinergic h.s. The patient had dramatic relief of ulcer symptoms, and to this date has not had a recurrence. In March the $CaCO_3$ was decreased to 4 gm. one hour p.c. and h.s.

The patient returned in early September relating a 2-3 week history of the following complaints, which he had taken care to write down on a piece of notepaper lest he omit one:

1) Weakness and fatigue, severe
2) A sense of depression
3) Severe constipation (previously he had had no constipation)
4) Nocturia x 2-4
5) Polydypsia and polyuria
6) Anorexia
7) Diffuse joint soreness and stiffness
8) Severe generalized headache
9) Generalized pruritus
10) "Shaky" legs

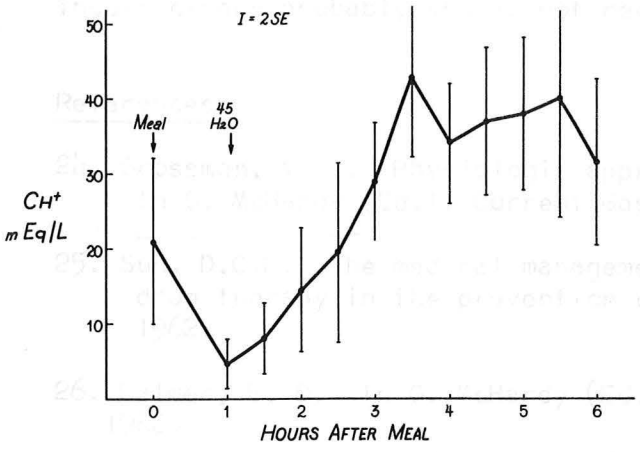
Exam at that time revealed no new findings; in particular, no band keratopathy was found. A history of previous renal disease could not be obtained. He stated that milk intake had been about 8 oz. tid, and that he had not taken soda.

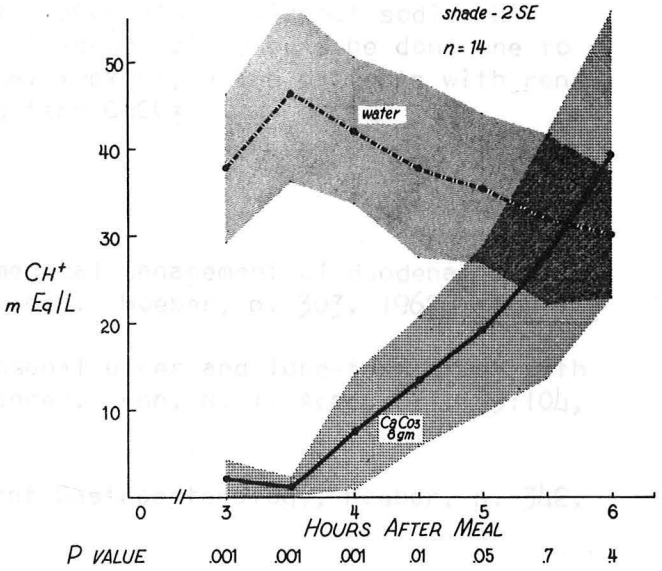
Laboratory data: Normal CBC and blood sugar; Ca 14.5 mg.%, PO_4 2.3 mg.%, CO_2 39, alkaline phosphatase 2.3 B.U. Urine specific gravity 1.010, hyaline casts 0-8/hpf, WBC 0-6, FBS 96 mg.%. Repeat Ca and PO_4 substantiated the hypercalcemia. A 24-hour urine calcium contained 108 mg. Ca (5.4 mEq.). while the patient was on a regular diet. Serum Na and K were normal.

The patient was instructed to eliminate calcium carbonate and milk, and AMT was prescribed.

The patient was seen again in 3 days, free of the above symptoms and with a serum Ca of 8.6 mg.% and PO_4 of 1.4 mg.%. Again, 4 days later the serum Ca was 9.9 mg.%. A 24-hour creatinine clearance test obtained 7 days after $CaCO_3$ was eliminated revealed a clearance of 60 cc. Calcium determination done on this same specimen showed 36.5 mg. of Ca (1.83 mEq.). A urine concentration test at this time revealed maximum concentration of 436 mOsm. A KUB done at the onset of these complaints failed to reveal calcium deposition in the kidneys.

The patient continues to do well at the present time.


I = 2 SE
Meal
45
H2O
CH+
m Eq/L
HOURS AFTER MEAL


shade - 2 SE
n = 14
water
CaCO3
8gm
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m Eq/L
HOURS AFTER MEAL
P VALUE
.001
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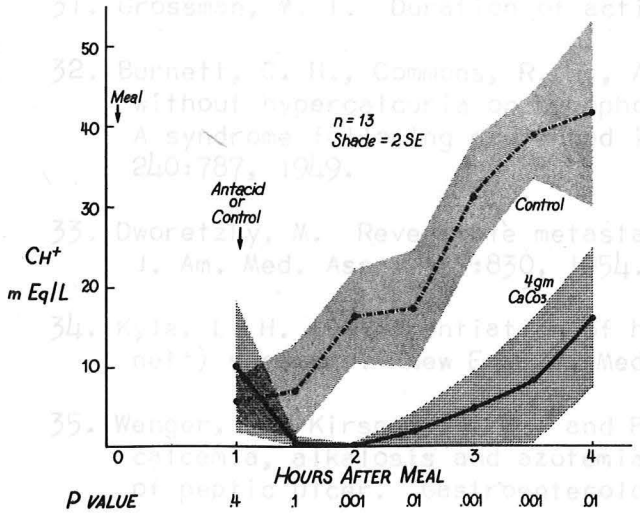
4


Meal
n = 13
Shade = 2 SE
Antacid
or
Control
Control
4gm
CaCO3
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m Eq/L
HOURS AFTER MEAL
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.1
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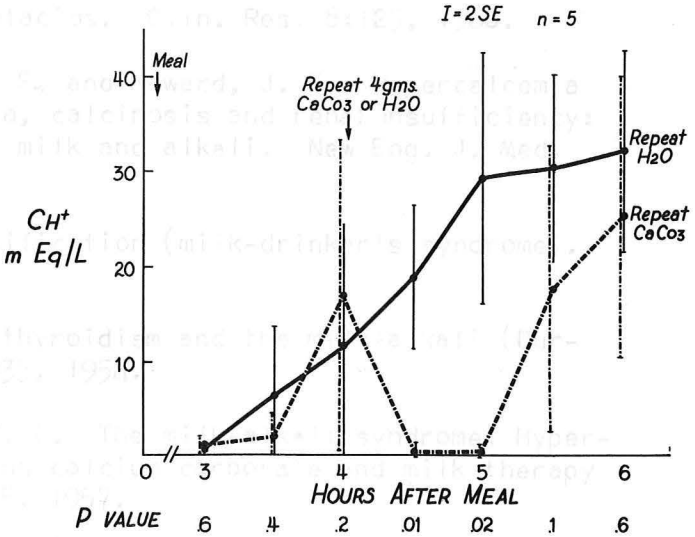
I = 2 SE
n = 5
Meal
Repeat 4gms.
CaCO3 or H2O
Repeat
H2O
Repeat
CaCO3
CH+
m Eq/L
HOURS AFTER MEAL
P VALUE
.6
.4
.2
.01
.02
.1
.6

The incidence of milk alkali syndrome due to $CaCO_3$ alone (without sodium bicarbonate and excess milk ingestion) is rare. A serum Ca^{++} should be done one to two weeks after starting $CaCO_3$ to detect its development,[24] and patients with renal insufficiency probably should not receive long-term $CaCO_3$.

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F. Radiation Therapy

1. History

Radiation therapy has been employed as an adjunct to the medical treatment of peptic ulcer, mainly by Palmer and associates of Chicago. No control studies are available.

2. Dose

Treatment is given to the fundus through an anterior and posterior port. The total dose is 1650 r, given in 14 days.[41]

3. Histologic Changes

Serial biopsy studies[42] have demonstrated a patchy gastritis following therapy. The initial injury occurs in the depths of the fundic glands. Coagulation necrosis occurs in the parietal and chief cells. The mucous neck cells proliferate and grow downward to replace the desquamated fundal glands. Certain areas undergoing radiation reaction have the appearance of gastric atrophy. At the peak of the reaction there is a marked increase of cellular infiltration in the interstitial tissue. The reaction reaches a peak in 3 to 6 weeks and subsides gradually, usually becoming completely normal within 4 months. Occasionally mild changes may persist for several years.

4. Effect on Gastric Acidity

The gastric secretory response to radiation therapy is variable.

a. "Histamine fast achlorhydria" was induced in 25 of 113 patients (23%); this lasted up to 6 months in 15, and from 6 months to 5 years in 10.

b. An additional 35 (34%) patients had greater than 50% reduction in acid secretion; duration variable.

5. Clinical Response

Clinical response depends to some extent on whether acid secretion is decreased or not.

Effect on Gastric Secretion	Clinical Response		
	Number of Patients	Ulcer Healed	Recurrence
Reduction less than 50%	53	51	20
Reduction greater than 50% for less than one year	45	45	13
Reduction by 50% or more for one year or more	15	15	5
Total	113	111	38

It is, of course, impossible to interpret these data in the absence of any control group. The authors believe that these patients generally did much better after x-ray therapy than before.

6. Contraindications:

a. Pyloric obstruction
b. Age ?

7. Long-Term Complications

114 of 723 patients with duodenal ulcer treated with radiation died at the time of last report (1957).[44] Follow-up was > 5 years. 8 deaths were attributable to peptic ulcer. 32 were due to cancer.

32 Cancer Deaths:

Stomach	4
Pancreas	4
Liver	1
Duodenum	1
Leukemia	0
Miscellaneous	22

No renal complications were reported from Palmer's group or by Bicks, et al.[45]

Conclusions:

1) X-ray therapy has not been subjected to control study.

2) The data suggest that healing of the ulcer will be facilitated and the incidence of recurrences reduced by radiation therapy.

3) The effect of radiation begins after several weeks of therapy, and lasts a variable length of time. Treatment can be safely repeated at least once.

4) The complications are minimal, but there may be an increased incidence of GI cancer following this therapy.

5) Not advisable if pyloric obstruction is present.

6) May be used for stomal and gastric ulcer as well as duodenal.

7) Use should be limited to patients over 50 years of age unless the patient is intractable and unfit for surgery.

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G. Suggested Medical Therapy for Uncomplicated Duodenal Ulcer

1. Instructions should be made with reference to charts and graphs, especially those on page 5 and Figures 1-4 of this protocol.

2. Diet: Three regular meals a day. Sanka or Postum instead of caffeine-containing drinks. Avoid alcohol completely for 6 weeks and then use as little as possible thereafter. Do not skip meals and do not eat at bedtime, which stimulates secretion through the night (and makes #3 ineffective).

3. Anticholinergics: Mouth-drying dose of anticholinergic at bedtime indefinitely. If patient wakes during the night, repeat.

4. Antacids: Use powder or liquid, not tablets. Give 1 and 3 hours p.c. and h.s. for 6 weeks. Then 1 hour p.c. and h.s. indefinitely. Use as large a dose as is practical.

5. Medications: Avoid aspirin completely. Give Darvon, etc., to keep at home in case of emergency. Avoid reserpine and butazoladine.

6. Follow-Up: Ascertain by direct questioning what patient is actually doing. Many patients misunderstand instructions.

If the patient does not respond to the above, re-evaluate diagnosis, rule out Zollinger-Ellison syndrome (maximum histamine test) and measure gastric secretory response after meals. Increase antacids if necessary.

There is no evidence that rest, abstinence from cigarettes, and sedative tranquilizers contribute to the management of uncomplicated duodenal ulcer. In some instances, their use is obviously appropriate.

This is basically the same program we use for gastric ulcer except that initially treatment is, in a sense, a diagnostic test to rule out cancer (by showing that ulcer shows definite healing in 5 weeks). Therefore, antacids should be hourly during waking hours during the early period, so that if healing does not occur, there will be no doubt about adequacy of therapeutic trial.