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PYLORIC FUNCTION, BILE REFLUX AND GASTRITIS

University — Université

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Degree for which thesis was presented — Grade pour lequel cette thèse fut présentée

M.Sc. EXPERIMENTAL SURGERY

Year this degree conferred — Année d'obtention de ce grade

FALL, 1981.

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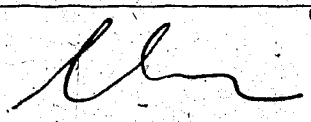

NL-91 (4/77)

THE UNIVERSITY OF ALBERTA

PYLORIC FUNCTION, DUODENOGASTRIC REFLUX AND GASTRITIS

By

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

DEPARTMENT OF SURGERY

EDMONTON, ALBERTA

FALL, 1981

THE UNIVERSITY OF ALBERTA

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TITLE OF THESIS Pyloric Function, Duodenogastric Reflux and Gastritis

DEGREE FOR WHICH THESIS WAS PRESENTED M.Sc.

YEAR THIS DEGREE GRANTED Fall, 1981

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FACULTY OF GRADUATE STUDIES AND RESEARCH

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PYLORIC FUNCTION, DUODENOGASTRIC REFLUX AND GASTRITIS

submitted by: DR. GERHARD KLASSEN

in partial fulfilment of the requirements for the degree of Master of Science.

Kenneth L Bowes
.....
SUPERVISOR

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Dedicated to my wife

Nancy

and our children

Anita

Benjamin

P. Joseph

Rebecca

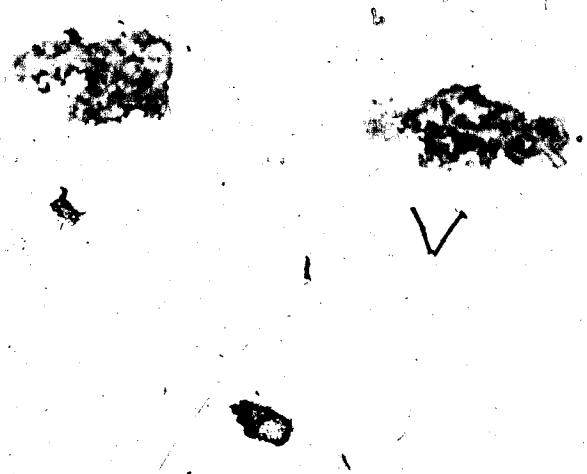
ABSTRACT

Duodenogastric reflux has been implicated in the pathogenesis of gastric ulcer and postgastrectomy syndromes. Pyloric dysfunction, idiopathic or post-surgical, is the postulated fundamental defect allowing reflux to occur. This study evaluated human pyloric pressures, quantitated bile reflux and gastric morphologic changes, and sought to establish correlations between these factors.

Pyloric pressure measurements were performed in ten normal human subjects using an infused catheter system. Duodenogastric reflux was studied in a separate group of 40 patients by radionuclide injection and by gastric content analysis for bile. The gastric fluid was collected at gastroscopy, followed by serial gastric mucosal biopsies for histologic analysis. Numerical scores were assigned to gastritic changes to facilitate patients groupings for correlations.

Manometric studies failed to demonstrate consistently a zone of elevated pressure at the pylorus, either at rest or after intraduodenal acid infusions. Duodenogastric reflux was demonstrated in four of 16 patients using radionuclide methods, and in 18 of 40 patients using gastric content analysis for bile. Gastritic scores increased significantly with age, as did the incidence of bile reflux. However, when matched for age, a significant positive correlation persisted between gastritis and duodenogastric reflux. Neither reflux nor gastritis could be correlated with symptoms.

This study demonstrated in unoperated patients the same association of duodenogastric reflux and gastritis as was demonstrated in gastric ulcer and post-operative patients. This strengthens the proposed etiologic role of refluxed duodenal content in effecting gastric mucosal changes.



ACKNOWLEDGEMENTS

I gratefully acknowledge the generous assistance of the following individuals in compiling and completing this thesis:

Dr. K.L. Bowes

Dr. W.M. Weinstein

Dr. H.T.G. Williams

Dr. R.H. Wensel

Dr. K. Walker

Dr. R.J. Bailey

Dr. L.D. Jewell

Dr. T.K. Shnitka

Mr. Ken Cote

Mr. Ian Simpson

Miss Jennie Cherwenuk

Miss Carol Shalapy

Mrs. Margaret McMullin

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INTRODUCTION

There is good reason to believe that gastritis is associated with duodenogastric reflux, but the body of evidence comes from studies of postoperative or gastric ulcer patients. The purpose of this investigation was to attempt to demonstrate this correlation in unoperated patients without ulceration. Several pertinent areas were assessed: pyloric function, presence of reflux, and gastric mucosal histology.

OBJECTIVES

1. To measure pyloric pressure.
2. To quantitate duodenogastric reflux in symptomatic unoperated patients.
3. To systematically examine gastric mucosal morphology in these patients.
4. To attempt to correlate gastric morphologic changes with duodenogastric reflux and with symptoms.

PYLORIC FUNCTION, DUODENOGASTRIC REFLUX AND GASTRITIS

(Introduction)

The role of bile in the stomach has been variously regarded as protective, unimportant or injurious to the gastric mucosa. The question of bile reflux has recently incited widespread interest, extensive speculation and diligent research. This review will discuss the evolution of current theories, the role of the pylorus, methods of quantification of duodenogastric reflux, and the effects of this reflux on the gastric mucosal barrier, and gastric histology.

I. HISTORICAL PERSPECTIVE

The classical studies on Beaumont[8] in 1833 are still frequently quoted. The gastric content of Alexis St. Martin was examined directly through a gastrocutaneous fistula. Beaumont found that bile was absent in health and was "only present during violent passion or when the antrum was irritated with a tube, or when pressure was applied over the duodenum or gallbladder". However, it was generally thought that reflux of alkaline substances served a protective function and played a role in regulating gastric acidity. (Boldyreff[15], 1914; Hick and Vishner[68], 1915; Olch[106], 1928).

It was noted that following gastric surgery or bile diversion there was a high incidence of stomal ulceration, which was attributed to the local absence of bile and pancreatic secretions to neutralize gastric acid. Operative procedures actually attempted to facilitate bile drainage into the stomach. (Braithwaite[18], 1943).

The introduction of vagotomy by Dragstedt[642] around 1940, and the subsequent widespread acceptance of this procedure based on a better understanding of gastric secretion brought serious doubts to the theorized protective role of bile. Furthermore, pioneer studies by Du Plessis[46] (1965), Capper[25] (1967), and Siurala and Tawast[126] (1955) found a much increased incidence of gastric bile in gastric ulcer patients than in normals or duodenal ulcer patients. The stage was then set for the opposing view - that bile was harmful to gastric mucosa and an etiologic factor in gastric ulceration. This revolutionary thought stimulated clinical and laboratory investigation. Technical advances improved histological and biochemical analysis. Nevertheless, arguments concerning the role of bile continue due to the complexity of the problem and the sometimes contradictory results.

II. THE PYLORUS: IS IT A SPHINCTER?

The thickened muscular ring located at the gastroduodenal junction has the name, "pylorus". The question of whether or not it constitutes a true sphincter is still open to debate. (Winans[139], 1976).

A. Anatomical Evidence

To the anatomist as well as the surgeon, the pylorus is represented by a definite palpable localized thickening of the gastrointestinal tract at the narrowest portion of the gastric outlet. This thickened area is circumferential, measures 1-2 cm in length, and impinges on the lumen. There is definite asymmetry starting gradually on the gastric side, becoming progressively thicker and ending abruptly on the duodenal side. (Torgerson[130], 1954). These factors suggest that the

pylorus must play a role in the regulation of gastric emptying, and prevention of duodenogastric reflux, i.e. it has the gross appearance of a sphincter. To the endoscopist the pylorus also is a definite entity. It is identifiable as a mural ring causing luminal narrowing and serving as a consistent landmark.

Histologically, the pylorus is found to be the zone of transition from gastric to duodenal mucosa, and shows a very characteristic muscular thickening which develops gradually on the gastric side, and which ends abruptly on the duodenal side, being separated from the circular muscle of the duodenum by a connective tissue septum, or "pyloric block". The longitudinal muscle coat of the stomach also thickens at the pylorus but much less so than the circular, and appears to have partial continuity with the corresponding duodenal muscle layer. The mucosal transition occurs more gradually in the same region as the connective tissue septum, and is identified by the appearance of duodenal or Brunner's glands. These glands effectively anchor the duodenal mucosa to the underlying muscularis, making it much less mobile than gastric mucosa. The gastric mucosa, because of its mobility, could prolapse into the pyloric ring, and perhaps act as a valve (Chapman[29], 1977).

Anatomic evidence, therefore, strongly suggests that the pylorus is a sphincter.

B. Functional Evidence

In contrast to anatomical considerations, the functional evidence favouring the presence of a pyloric sphincter is surprisingly weak. Manometrically, a sphincter is a zone of tonically elevated pressure

with precise episodes of opening, as for example the lower esophageal sphincter. Attempts to measure pyloric pressure have met with limited success. Five studies using the balloon in man and dog failed to demonstrate a tonic contraction of the pyloric ring (Whelan and Thomas[136], 1920; Brody et al[20], 1940; Quigley et al[111], 1942; Atkinson et al[4], 1957; Anderson and Grossman[1], 1965). However, by combined use of balloons and side-hole open tipped tubes, Brink et al[19] (1965) found a zone of high pressure at the canine gastroduodenal junction. Similar results were obtained by Isenberg and Csendes[72] (1972).

Using the open-tipped perfused catheter system, Fisher and Cohen[54] (1973) and Fisher, Lipshutz and Cohen[55] (1973), on normal human subjects in the right decubitus position, demonstrated a basal elevated resting pyloric pressure of 3.8 ± 0.3 mm Hg (mean ± S.E.M.). Valenzuela and coworkers[132] used similar methods and found pyloric pressure to be about 10 mm of mercury. Kaye, Mehta and Schowalter[78] (1976), using both a miniature transducer assembly and perfused catheters, and with the subject supine, were unable to demonstrate consistently a zone of tonically elevated pressure. Pandolfo et al[109] (1979) studied the human gastroduodenal junction for prolonged periods and concluded that the pylorus was not tonic in the resting state, but they were able to demonstrate a zone of elevated pressure after duodenal acidification.

The conflicting results may be due to different methodologies. Various tube and balloon assemblies may not be equally suitable, although tube diameters were very similar. Furthermore, the position of the subject, whether supine or right lateral decubitus, probably alters

the anatomic configuration of the gastroduodenal region, as argued by Kaye et al[78] (1976), thereby giving divergent results. Finally, the methods of analysis of the results varied thereby leading to different conclusions based on similar recordings.

Somewhat more convincing and more interesting is the finding that the pyloric region reacts to exogenous drugs and hormones, and to endogenous hormones. The C-terminal octopeptide of cholecystokinin was shown to increase the resting tone of the pyloric high pressure zone in dogs (Isenberg and Csendes[72], 1972). Brink, Schlegel and Code[19] (1966) demonstrated increased pressure of the canine pylorus following intraduodenal acid and olive oil infusions. In man, pyloric pressure increased in response to intraduodenal infusion of 0.1 N HCl, olive oil and amino acids, which are known to release secretin and cholecystokinin (Fisher and Cohen[54], 1973; Valenzuela et al[132], 1976; Pandolfo et al[109], 1979). Once again, Kaye et al[78] (1976) and Quigley[111] (1942) were unable to demonstrate any significant response to acid or olive oil administration. Exogenous secretin and cholecystokinin increased human pyloric pressure (Fisher and Cohen[54], 1973-6) as did metoclopromide (Valenzuela et al[132], 1976) and insulin-induced hypoglycemia (Fisher et al[56], 1979). In a combined *in vivo* and *in vitro* study using human volunteers and opossum pyloric muscle, Fisher, Lipshutz and Cohen[55] (1973) examined the effect of several gastrointestinal hormones. Gastrin I had little effect on the pylorus, but both cholecystokinin and secretin were agonists with an additive effect at submaximal concentrations. Gastrin I produced a competitive-like antagonism

to the effect of cholecystokinin on pyloric muscle.

The mechanism of response to duodenal acidification is generally thought to be hormonal, but his may be incorrect. The pressure response is almost immediate, whereas the response to olive oil is delayed about fifteen minutes (Brink et al[19], 1965). Furthermore, the response to acid is quickly abolished with atropine, thus favouring a neurogenic or direct pathway. Endogenous release of secretin and cholecystokinin has been demonstrated (Barbezat[7], 1971) and probably also plays a role.

C. Pyloric Dysfunction

Attempting to correlate pyloric function and disease states is greatly hampered by the disparity of findings in normal subjects. It is postulated that pyloric dysfunction allows reflux of duodenal contents into the stomach, which in turn causes gastric mucosal damage. Gastric ulcer patients have served as a model to test this hypothesis. Munk et al[103] (1976) found that gastric ulcer patients had a larger pyloric diameter, lower pyloric pressure and decreased response to cholecystokinin when compared with duodenal ulcer patients and normals. Fisher and Boden[53] (1975) demonstrated low-normal resting pyloric pressures in gastric ulcer patients. This pressure however, failed to rise in response to duodenal acid or fat, as seen in normal controls. After gastric acidification, the response became normal. The effect of ulcer healing on pyloric response was not described.

Anatomic alterations of the pylorus have also been incriminated in gastric ulcer patients. A thickened pylorus with associated luminal narrowing has been demonstrated and thought to cause delayed gastric

emptying and consequently increased acid secretion (Burge[22], 1966; Dragstedt and Woodward[44], 1970). Recent anatomical studies of the antrum and pylorus have shown that patients with gastric ulcer have hypertrophy of the muscle, submucosa and mucosa, with occasional fibrous narrowing compared to controls (Liebermann-Meffert and Allgöwer[93], 1974). This antral-pyloric hypertrophy could be primary or secondary, and suggests an associated motility disorder. Davenport[34] (1967) showed in Heidenhain pouches that aspirin in an acid solution increased motility in the pouch, and this was presumed to be due to increased back diffusion of hydrogen ions. Bile releases gastrin from antral mucosa and, in human subjects, increases antral contractions (Misiewicz et al[102], 1969). Garrett, Summerskill and Code[60] (1966) found abnormal gastric motility in gastric ulcer patients. The data regarding this question is still rather speculative.

D. Electrophysiological Evidence

Membrane potential in the gastrointestinal tract is a reflection of qualitative differences in the epithelium. An abrupt change in potential difference (PD) reflects a change in types of cells. Anderson and Grossman[1] (1965) developed a technique whereby the mucosal duodeno-gastric junction could be identified as a sharp change in potential difference, as measured by a catheter filled with a conducting medium. The antral mucosal potential difference is about 21 mv more negative than duodenal mucosa in the dog, and about 27 mv in man. Others have used the same basic principle in manometric studies to identify the pylorus. (Fisher and Cohen[54], 1973; Kaye et al[78], 1976; Valenzuela[132], 1976; Hernandez[67], 1969; Fisher, Lipshutz and Cohen[55], 1973-76.)

Antral-pyloric-duodenal co-ordination is a complex area and has been studied in detail. (Carlson[28], 1966; Sarna[121], 1979; Hiesinger[69], 1979).

There are two components to electrical activity in stomach and duodenum. The first is always present, and is a recurrent cyclic slow fluctuation in potential, usually referred to as 'slow wave' or the basic electrical rhythm (BER). It continues regardless of contraction or relaxation of the stomach. The second is the spike potential which initiates gastric contraction. It occupies a specific segment of the slow wave and one burst of spike potential occurs in slow wave. A spike potential is always associated with a BER cycle, but not every BER cycle produces a spike (Chapman[29], 1977).

Despite the fact that there is almost complete muscular separation between stomach and duodenum, some electrical activity appears to be co-ordinated across the junction. This was illustrated in the guinea pig after tetratoxin (Fujii[58], 1971) and the dog by circumferential transection and mucosal sparing (Bedi and Code[9], 1972). Stoddard[128] (1976) thought that in humans the pylorus did not act as an electrical insulator.

Pyloric muscle does have distinct properties that are peculiar to itself. Anuras, Cooke and Christiansen[3] (1974) found that electrical field stimulation produced relaxation of pyloric muscle strips but not adjacent gastric or duodenal muscle. A distinctive neural inhibitory control mechanism for pyloric muscle was suggested on the basis of pharmacologic manipulations of the tissue. Similar conclusions were

drawn by Golenhofen[63] (1979) who also attempted to separate the pyloric muscle into inner and outer layers. Interestingly, both he and Ehrlein et al[50] (1979) found no pyloric response to secretin or cholecystokinin as has been suggested by clinical work.

The role of the pylorus particularly with respect to its sphincteric function, is not at all elucidated. The apparent anatomical and pharmacologically distinct muscular ring does not appear distinct when examined electrically. Manometric studies are inconclusive. Perhaps the pylorus will not conform to a rigid definition of a sphincter applied to other regions of the gastrointestinal tract, but further studies concerning its function may help to define its role more accurately.

III. DUODENOGASTRIC REFLUX

The normal anatomic configuration of the gastrointestinal tract is such that bile and pancreatic juice are secreted into the duodenum distal to the pylorus. The appearance of these substances in the stomach, therefore, indicates retrograde or orad flow along proximal duodenum, and across pylorus, hence the term "duodenogastric reflux". Alteration of the anatomic pattern by surgical procedures may be reflected by physiologic and pathologic changes.

Duodenogastric reflux may be assessed endoscopically, radiologically or biochemically.

A. Endoscopic Assessment of Reflux

As noted previously, Beaumont[8] (1833) had direct access to the stomach of his patient through a large chronic gastrocutaneous fistula.

He noted that bile was rarely present. Normally, however, the stomach is accessible only surgically or by passage of tubes or instruments along the esophagus. The greatest technical advance in this regard has been the introduction of the flexible fibreoptic gastroscope, which allows accurate inspection and sampling of fluid and tissue.

Duodenogastric reflux can be identified by positioning the gastroscope in the antrum and observing the pylorus. (Scudamore et al[123], 1973; Munk et al[103], 1976; Koelsch et al[86], 1978; Lechner[91], 1975). Some patients may have reflux vigorously producing a jet of fluid across the pylorus (Eckstrom[48], 1974). Goldner and Boyce[62] (1975) found that endoscopic grading of degree of bile staining found in gastric fluid correlated well with total bile acid concentrations.

Endoscopic criteria for reflux or mucosal status are subjective and impossible to standardize. In order to draw comparisons between studies it is important to obtain appropriate samples for more objective analysis. It is also necessary to attempt to standardize and to describe the conditions under which a study was performed. The position of the patient and administration of premedication, for example, could influence the results obtained. It is quite conceivable that the presence of the gastroscope itself affects reflux and thus other methods of evaluation need to be explored.

B. Radiological Assessment of Reflux

Duodenogastric reflux may be assessed radiologically by using contrast material or isotopes. Beneventano and Schein[11] (1970) performed T-tube cholangiograms in 36 patients and found that one third of them

refluxed some of the contrast material into the stomach. The conclusion that this reflux could be physiologic was challenged by Feinberg and Delaney[51] (1974), who found reflux in only two of 148 T-tube cholangiograms.

Capper, Airth and Kilby[26] (1966) introduced the "*pyloric regurgitation test*" which involved the placement of a small tube into the duodenum followed by barium injection and observation of the stomach. Reflux was graded as absent, mild, moderate or severe. Their technique was later modified by dilution of the barium before instillation (Cocking and Grech[31], 1973). Unfortunately, the "*pyloric regurgitation test*" requires the use of a tube which crosses the pylorus and could thereby influence pyloric function.

Several radioisotope techniques have been devised to quantitate reflux. Rhodes et al[114] (1969) used ^{14}C-labelling of the bile acid pool to measure bile acid concentrations in gastric samples obtained by aspiration. This technique seemed better because the pylorus remained uncompromised. However, it still necessitated the introduction of a tube into the stomach for collection of samples.

Sonnenberg et al[127] (1979) used isotope labelling in dogs to study gastric emptying and duodenogastric reflux.

A new and perhaps superior technique was described by Tolin et al[129] (1969). This method involved intravenous administration of 5 μCi ^{99m} Technetium (Tc) bound to iminodiacetic acid (IDA) and later oral administration of 250 μCi ^{111}Indium bound to diethylene-triamine-penta-acetic acid (DTPA). The ^{99m} Tc-IDA was secreted in the bile and

could be observed by scintigraphic imaging. (Harvey[65], 1975; Rosenthal[120], 1978; and Loberg[94], 1979). The ^{111}Indium-DTPA was used to outline the stomach. By computer analysis it was possible to quantitate reflux based on the distribution and number of counts obtained. This technique seems superior to other methods because it is tubeless and quantitative, but more experience is required before its validity can be widely accepted.

C. Biochemical Assessment of Reflux

The bulk of the literature concerning methods of assessing duodeno-gastric reflux involve analysis of gastric content for the presence of endogenous or exogenous markers.

The commonest endogenous marker used is bile. The presence of bile in the gastric aspirate has been identified by yellow or green discoloration (James and Pickering[74], 1949; Watkinson[134], 1951; Goldner[62], 1975; Lechner[91], 1975). Although visual inspection of the fluid for bile is fairly accurate when moderate or large amounts are present, it is unsatisfactory at low concentrations (Goldner[62], 1975). Scudamore et al[123] (1973) and Koelsch et al[86] (1978) combined visual and biochemical analysis to establish the presence of bile. Du Plessis[46] (1965) used paper chromatography to identify bile acid conjugates. Rhodes et al[114] (1969) measured ^{14}C-labelled chenodeoxycholic acid in gastric aspirates as mentioned previously. Enzymatic analysis using steroid dehydrogenase was used by Black et al[14] (1971) and by Hoare et al[71] (1978). Bile acids are stable in an acid medium and therefore accurately assessed at various pH levels. Bilirubin as assessed by icteric index is somewhat unstable in an acid environment and therefore should be evaluated early

(Wormsley[141], 1972; Scudamore et al[122], 1973; and Keighley[79], 1975). Furthermore, acid samples must be cleared with sodium hydroxide before colorimetric estimation for bilirubin can be performed.

A variety of endogenous markers other than bile have been measured. Wormsley[141] (1972) measured bile pigment as icteric index, bicarbonate concentration, and trypsin as proteolytic activity. Both bicarbonate concentration and trypsin activity were influenced by the degree of gastric acidity and therefore should be considered less reliable indices of reflux. Other endogenous markers such as sodium concentration have been tried (Fiddian-Green et al[52], 1979) but these lack specificity. Recent attention has been turned to lysolecithin, a product of pancreatic phospholipase A reacting with biliary lecithin. (Johnson and McDermott[76], 1974; Orchard[107], 1977).

The obvious advantage to using endogenous markers of reflux is their ready availability, but unfortunately it is impossible to control for biologic variability. Several workers have therefore administered exogenous markers of known amount and then measured the fraction which refluxed. Bromsulphthalein and Indocyanine Green are secreted in the bile and can be measured in gastric fluid (Fiddian-Green et al[52], 1979). These substances are dependent on delivery to the duodenum via the biliary tree at the time that samples are taken, and therefore subject to the same criticisms as bile analysis.

A different technique involves intraduodenal infusion of an exogenous marker with simultaneous antral aspiration to determine whether reflux is occurring. Wormsley[141] (1972) used this method and infused

polyethylene glycol; Fisher and Cohen[54] (1973) used phenol red as a marker; and Rokkjar[119] infused a radiolabelled marker . These experiments facilitate mathematical calculations and comparisons between groups of subjects, but the one disadvantage again is the necessity of a transpyloric tube. In an animal model with distal access to the duodenum, as for example, through a Thomas cannula in the dog, this method is ideal.

IV. GASTRIC MORPHOLOGY

A. Normal Gastric Mucosa

The gastric mucosa when examined grossly is moist, mobile and beige to pink in colour. It is soft and thick giving the appearance of a very fine, rich plush carpet, undulating over the underlying rugae of the body while being relatively flat in the antrum. Endoscopically it is more difficult to judge mucosal colour, but in the normal state it should be relatively uniform without patchy redness or granularity. Gastritic mucosa should be suspected when the vascular pattern is easily recognizable (atrophic) or when there is marked granularity or patchy redness (acute superficial). However, the endoscopic diagnosis of gastritis is notoriously inaccurate, and must be substantiated by biopsies (Goldner[62], 1975; Keighley et al[79], 1975; Hoare[70], 1977).

The normal histologic appearances of gastric mucosal biopsies have been described and illustrated by Whitehead[137] (1977). In the subsequent chapter of the same book, as well as in a separate publication (Whitehead et al[138], 1972), he presents a workable classification of

gastritis based on mucosal type, grade and activity of the gastritis, and presence of metaplasia. Schrager et al[122] (1967) have described antral changes found in duodenal and gastric ulcer patients.

B. The Gastric Mucosal Barrier

Man has been intrigued by the discovery that the stomach is capable of secreting acid and pepsin for digestion but appears immune to autodigestion (Dragstedt[43], 1978). A great volume of literature has accumulated concerning this property called the gastric mucosal barrier (GMB). The gastric surface epithelium is relatively impermeable to certain ions, especially hydrogen and sodium. Maintenance of the GMB requires intact epithelial cells and may be assisted by an overlying layer of mucus.

A variety of animal models have been used: dog (Davenport et al[33], 1964; Werther et al[135], 1970; Black et al[13], 1971; Ritchie[117], 1976); rabbit (Birkett and Silen[12], 1974); mouse (Eastwood[49], 1975); and guinea pig (Orchard et al[107], 1977). Human subjects have also been studied (Ivey et al[73], 1970; Chapman et al[30], 1972). The most extensive studies of the GMB have been performed by Davenport and his colleagues who demonstrated increased transmucosal flux of hydrogen, sodium and potassium after exposure of canine gastric mucosa to a variety of agents including eugenol, acetylsalicylic acid, ethanol, bile, taurocholate, urea, lysolecithin and digitonin. (Davenport[33, 35-38], 1964, 1965, 1968, 1970, 1975). The work of other authors confirm his results, especially with regard to the effects of bile (Werther[135], 1970; Ivey[73], 1970; Ritchie[115], 1975; Eastwood[47], 1975; Birkett and Silen[12], 1974; Black,

Hole and Rhodes[13], 1971) and of lysolecithin (Orchard[107], 1977; Johnson and McDermott[76], 1974). Davenport, Werner and Code[33] (1964) also found that an abrupt change in mucosal potential difference occurred which paralleled the increased ionic permeability. Histological damage can also be detected after exposure of gastric mucosa to bile or other agents (Lawson[88], 1964; Delaney et al[40], 1975; Eastwood[47], 1975). Tissue damage is related to hydrogen ion back diffusion and will not occur if the gastric content is of neutral pH. Histamine has been implicated as a mediator of tissue damage because damage can be prevented by combined use of H_1 and H_2 receptor antagonists. (Rees et al[113], 1976).

C. Clinical Observations and Studies

The pathogenesis of gastric ulcer and gastritis has been the subject of vigorous debate for many years. Whereas excess gastric acid secretion is an important factor in duodenal ulcer disease, gastric ulcer patients characteristically secrete normal or below normal levels of acid. The presence of acid may play an important role (Dragstedt[43], 1978), but other factors must be considered, particularly mucosal resistance and presence of duodenogastric reflux.

Careful histological examination of gastric ulcer specimens is mandatory to exclude the diagnosis of malignancy. However, it has been found that gastric ulcer usually occurs in abnormal mucosa (Magnus[95], 1938; Hebbel[66], 1943; Guiss and Stewart[64], 1948). Schrager, Spink and Mitra[122], (1967) and Du Plessis[46] (1965) have demonstrated that diffuse inflammatory and epithelial changes are nearly always present in the

mucosa of the gastric ulcer patients. The relative size of the pyloric gland area and extent of the gastritis are increased if the ulcer is more proximal in the stomach (Ball and James[6], 1961; Capper[25], 1967; Oi, Oshida and Sugimura[105], 1959). The increased hydrogen ion absorption in gastric ulcer patients demonstrated by Chapman et al[30] (1972) could be a function of an unusually extensive pyloric gland or antral mucosa which is normally somewhat more permeable to ions than fundic mucosa. The co-existence of gastric ulcer and gastritis suggests the possibility of a common etiologic mechanism.

Beaumont[8], from his study of Alexis St. Martin in 1833, stated "Bile is never found in the gastric lumen in a state of health". Watkinson[134] (1951) found that bile staining was invariably present in cases of gastric ulcer where nocturnal neutralization occurred. Pickering and James[74] (1949) showed that bile-stained gastric aspirate was more common in patients with gastric ulcer than in healthy people. Du Plessis[46] (1965) and Buckler[21] (1965) also demonstrated increased incidence and concentration of gastric bile in gastric ulcer patients versus controls. Rhodes et al[114] (1969) used ^{14}C-labelling of the bile acid pool to measure bile acid concentrations in gastric samples and found elevations in gastric ulcer patients while fasting and after a liquid meal, as compared to normal subjects. Reflux was accentuated by feeding and was more marked in the distal stomach than the fundus. Black, Roberts and Rhodes[14] (1971) were unable to show accentuation of reflux by a liquid meal, and furthermore found no consistent change in bile reflux with ulcer healing.

The pyloric regurgitation test described by Capper, Airth, and

Kilby[26] (1966) gave similar results: 19 of 29 gastric ulcer patients demonstrated gross duodenogastric reflux but none of 15 controls. He described active reflux visualized fluoroscopically and occurring with vigorous duodenal antiperistalsis. Other clinical studies have employed Capper's technique and found reflux in nine of 27 patients with duodenal ulcer, and in six of eight patients with atrophic gastritis. (Capper, Butler and Buckler[27], 1966); in seven patients with chronic alcoholic gastritis (Flint and Grech[57], 1970); and in 17 of 19 patients with chronic non-specific lung disease (Beeley and Grech[10], 1971).

Finally, exogenous marker infusion techniques employed by Wormsley[141] (1972) and Fisher and Cohen[54] (1973) also demonstrated increased duodenogastric reflux in gastric ulcer patients. Duodenal ulcer patients also showed reflux above control levels, but much less than gastric ulcer cases, confirming the results of Capper et al[27] (1966).

The clinical studies give convincing evidence for the association of bile reflux and gastric ulcer, and the GMB experiments implicate bile as an etiologic factor. But what about gastritis? Is bile reflux increased in, and possibly the cause of, gastritis? Direct evidence in this regard is rather weak, but additional clues are suggested by animal experiments and post-operative human studies.

Gastritis is a common finding and increases with age (Andrews et al[2], 1967; Kimura[84], 1972; Kekki et al[81], 1977). It may be caused by mucosal irritants such as acetylsalicylic acid (Davenport[34], 1967; Metzger et al[100], 1976); alcohol (Palmer[107], 1954; Kekki et al[81], 1977) and the drinking of hot liquids (Edwards and Edwards[49], 1956). The high

incidence of gastritis in gastric ulcer patients has already been discussed. Gastritis, particularly the atrophic form, is also found in patients with parietal cell or intrinsic factor antibodies and is a constant finding in pernicious anemia (Glass[61], 1977). Apparently normal totally asymptomatic human subjects have a significant incidence of gastritis as demonstrated by Kreunig[87]. All of these factors must be taken into account when studying gastritis.

Bile reflux has been noted in association with gastritis (Capper, Airth and Kilby[26], 1966; Siurala and Tawast[126], 1956; Capper[25], 1967; Kleckner et al[85], 1972; Scudamore et al[122], 1973). The main problem in evaluating clinical studies concerning this topic is the lack of uniformity of protocol between different authors and even within individual studies. Criteria for patient grouping are often ambiguous. For example, the study reported by Scudamore et al[123] (1973) seems to classify patients as refluxers on the basis of endoscopic observations, *or* presence of bile staining at the time of gastric fluid analysis. The fluid apparently was not analyzed for the actual presence or concentration of bile. Their diagnosis of gastritis was made in a variety of ways. Since 42 cases are described, but only 36 histological specimens were obtained, it must be assumed that subjective criteria depending on endoscopic appearance were involved at least part of the time. Furthermore, the 36 specimens were partly derived from surgical resection procedures and partly from gastroscopic mucosal biopsies, but the numbers are not specified. Their conclusion that all patients had chronic gastritis may, therefore, not be adequately substantiated.

A German paper by Lechner[91] (1975) has attempted to correlate bile

reflux with various gastric lesions. This study included 400 unoperated patients who underwent gastroscopy. Bile reflux was considered present when either it was observed directly through the gastroscope *or* there was significant yellow or greenish discolouration of the gastric pool. Again, the visual impressions were not authenticated by biochemical analysis. Using these criteria, he found that 17% of the 400 subjects showed evidence of bile reflux. There were no significant differences between sexes or age groups. Mucosal biopsies were taken from all patients but their location or number was not specified. Endoscopically, 146 of 400 were considered normal but histologically only 54 of 400 were called normal. However, he found that bile reflux occurred just as frequently in normals as in abnormals, and that the incidence of reflux did not vary significantly between groups of patients (normal, duodenal ulcer, gastric atrophy, erosions, gastric ulcer, carcinoma, hiatus hernia with ulcer). Finally, he also attempted to correlate type of gastritis with presence of bile reflux, and again found no difference.

Koelsch et al[86] (1978) have performed a study which is also published in German, but produced very different results. The study consisted of 221 patients undergoing gastroscopy for dyspepsia of undefined cause. Gastric fluid was aspirated and analysed for total bile acid concentration followed by thin-layer chromatography for bile acid fractionation. Serial mucosal biopsies were taken. A patient was considered to have bile reflux if (a) duodenal regurgitation was observed gastroscopically, (b) gastric fluid analysis for bile was positive, *or* (c) bilious discolouration of gastric fluid was noted on gastric analysis. Unfortunately,

it is unclear whether all patients underwent gastric aspiration and analysis at gastroscopy, or how many patients were classed as refluxers under criteria (a) or (c) above. Duodenogastric reflux was said to be present in 58.8% of all patients. The incidence of reflux and the concentration of bile both increased with age. Two thirds (8 of 12) gastric ulcer patients were found to have reflux, as compared to 6 of 7 (85.7%) duodenal ulcer patients, and 6 of 13 (46.1%) patients with erosive gastritis. The incidence of reflux was about 60% for chronic superficial gastritis (42 of 70) as well as for chronic atrophic (29 of 47). Whereas Lechner[91] found no difference in reflux between cholecystectomized and unoperated patients, Koelsch and colleagues reported reflux in 81% of cholecystectomized patients (30 of 37) as opposed to 54.3% of non-cholecystectomized patients (100 of 184). Heavy smokers with reflux had a significantly higher incidence of chronic gastritis than non-smokers with reflux. However, when considering all smokers versus light or non-smokers, the difference in incidence of chronic gastritis was not significant.

Goldner and Worth Boyce[62] (1975) studied 48 patients and found no correlation of bile acid concentration with histologic evidence of gastritis.

Clinical studies attempting to correlate duodenogastric reflux and gastritis thus far have produced unpredictable and conflicting results.

D. Animal Experiments

Much of our knowledge concerning the gastric mucosal barrier comes from various animal studies. However, special mention must be made of several ingeneous experiments designed to study the effects of chronic exposure to bile. Lawson[88] (1964) studied the effects of bile and pancreatic juice on canine gastric mucosa by surgically diverting these substances into the stomach. The gastritis was most marked near the site of entry and was more severe with both bile and pancreatic juice, but least with pancreatic juice alone. Definite histologic changes comparable to human gastritis were reported. These changes were later shown to be reversible by diverting bile away from the stomach (Lawson[90], 1972).

Delaney et al[40] (1975) constructed tubes of canine gastric corpus in such a manner as to allow chronic exposure to jejunal contents, to pancreatic juice or to bile. Marked gastritis was reported under all conditions but whole jejunal contents were found to cause more severe changes than pancreatic juice or bile separately.

Atrophic gastritis has been induced in dogs by explanting parts of the stomach (Lawson[90], 1966; Ritchie and Delaney[118], 1971). Reimplantation of damaged mucosa into the stomach was shown by the same authors to cause an increased incidence of gastric ulcers in the affected portion. This is suggestive evidence of increased susceptibility to ulcer formation in abnormal or gastritic mucosa.

The concept that bile is deleterious to gastric mucosa has not been accepted unanimously. Byers and Jordan[24] (1962) implanted

vascularized patches of gastric mucosa into the wall of the gallbladder in dogs. After a year the mucosa was histologically normal. Bile alone, therefore, does not appear to be responsible.

Dragstedt's treatise[43] (1978) on the pathogenesis of duodenal and gastric ulcers still favours the concept of a protective function afforded by bile and pancreatic juice. His reasons are twofold. First of all, patients undergoing Roux-en-Y procedures for peptic ulcer have a high incidence of stomal ulceration. Secondly, animal experiments by Mann and Williamson[96] by McCann[97] (1927) and by Dragstedt et al[45] (1971) causing bile diversion into the gastric fundus or into esophagus failed to reveal gastric or esophageal ulcers, only stomach ulcers distally. Unfortunately, histological evidence of gastritis under these circumstances was not sought. The cumulative data in postoperative patients favours the former hypothesis that duodenal juice is in fact injurious to gastric mucosa, rather than protective, as will be discussed next.

E. Postoperative Studies

It was previously noted that bile reflux occurred infrequently in normal subjects, and this was attributed to a functioning pylorus. Any operative procedure which removes or otherwise interferes with pyloric integrity, then, would be expected to induce reflux. Borg[17] (1959) and Du Plessis[46] (1965) reported frequent severe bile reflux after Billroth II gastrectomy. Kilby[83] (1970) used Capper's method to assess duodenogastric reflux in 30 patients who had undergone pyloroplasty and a further 15 after pyloric resection (Billroth I). He observed reflux in all of these subjects but suggested that any operation

on the pylorus reduced the force with which reflux occurred. Keighley et al[79] (1975) measured reflux radiologically and by bilirubin screening and found reflux in 12% after proximal gastric vagotomy, 45% after vagotomy and pyloroplasty, and 78% after vagotomy and antrectomy. Hoare et al[71] (1978) found elevated levels of bile acids in post-gastric surgical patients and attempted to quantify the reflux during a specific time interval (Fasting Rate of Bile Reflux).

Gastritis is frequently present after gastric surgery (Palmer[108], 1954) and its extent and severity increase with time following surgery (Johnston[77], 1966; Aukee and Krohn[5], 1972). The site of the gastritis was variable but corresponded to areas where duodenal contents had access to the stomach (Capper, Butler and Buckler[27], 1966). Lees and Grandjean[92] (1958) studied patients who had undergone a Polya type gastrectomy for benign ulcer disease performed within five years. In 32 of 33 patients inflammatory changes were present. Both Du Plessis[46] (1965) and Capper[25] (1967) concluded that gastritis was caused by bile regurgitation.

V. BILE REFLUX, GASTRITIS AND SYMPTOMATOLOGY

Patients with reflux or gastritis may present clinically with a variety of non-specific symptoms, but these may be difficult to evaluate because apparently normal subjects may have similar symptoms. Also, totally asymptomatic patients may be shown to have the same degree of reflux or grade and extent of gastritis. (Shiner and Doniach[125], 1957; Coghill[32], 1960; Beeley and Grech[10], 1971; Lees and Grandjean[92], 1958). Recently however, because of the severity and persistence of postoperative

symptoms, a number of clinical studies have been carried out. (Boren and Way[16], 1980; Davidson and Hersh[39], 1980; Menguey and Chey[100], 1980; Ritchie[116], 1980).

Keighley et al[79] (1975) studied 35 patients who had previously undergone surgery for peptic ulcer disease. Those patients with high concentrations of bilirubin in gastric juice frequently complained of bile vomiting, nausea, epigastric pain after meals, bile regurgitation and heartburn. These symptoms were infrequent in patients with low concentrations of bilirubin in the gastric aspirate. A further study by Keighley and his colleagues[80] (1975) of 63 postoperative patients found an association between the degree of reflux and the presence of severe heartburn, epigastric pain and bilious vomiting. The term, postoperative alkaline reflux gastritis was introduced by van Heerden et al[133] (1969). Toye and Williams[131] (1965) described and illustrated a severe case of postoperative bile reflux. Scudamore[123] (1973) as well as Bushkin[23] (1974) describe the syndrome of postoperative alkaline reflux gastritis as being characterized by postprandial severe mid-epigastric pain unrelieved by antacids, but relieved promptly and completely by bilious vomiting. It is usually associated with weight loss, hypochlorhydria and atrophic gastritis.

Pyloric regurgitation was correlated with symptoms in 40 patients without previous gastric surgery by Johnson[75] (1972). His diagnosis of flatulent dyspepsia correlated well with pyloric regurgitation, and this could perhaps explain one mechanism behind post-cholecystectomy syndromes.

Several factors are known to affect the incidence of duodenogastric reflux. Operative procedures have already been discussed. Reflux is less common in supine than erect patients (Flint and Grech[57], 1970) and this has been attributed to decreased duodenal motor activity (Capper[25], 1967). Cigarette smoking was found to decrease pyloric sphincter pressures (Valenzuela et al[132], 1976). Smoking also increased reflux in gastric ulcer patients (Dippy, Rhodes and Cross[41], 1973), and in normal and dyspeptic subjects (Read and Grech[112], 1973). Theoretically one would expect metoclopramide to reduce reflux by improved antroduodenal co-ordination, but this could not be substantiated by Dippy, Rhodes and Cross[41] (1973). Marked reflux of bile into the stomach was produced in three normal subjects by the intravenous administration of Prostaglandin E, but the mechanism or significance of this finding is unknown. Duodenogastric reflux is readily produced by retrograde duodenal pacing in the dog (Kelly et al[82], 1979) and the cat (Munk and Johnson[104], 1979). This finding is not surprising, and confirms that reflux can be produced by disordered motility.

VI. SUMMARY

Pyloric pressure studies in normal subjects have produced widely discrepant results. This appears to be a function of the organ of study rather than faulty experimental design. Pressures are low and inconstant making quantitation difficult. The concept of decreased pyloric pressure or responsiveness allowing reflux to occur as the basic etiologic factor in the pathogenesis of gastric ulcers is theoretically

appealing. Perhaps the same underlying process is responsible for gastritic changes. However, these conclusions are premature and await further elucidation of pyloric function in normal and in disease states.

There is general agreement in the literature that duodenogastric reflux is increased in gastric ulcer and postgastrectomy patients. The fact that consistent data was derived by a variety of experimental techniques suggests that the findings are valid for that population. The studies attempting to correlate the presence of reflux with gastritis, however, are surprisingly few. Poor study design and insufficient numbers of subjects precludes widespread acceptance of any apparent correlation. Furthermore, the opposing view that reflux of duodenal content is not injurious to the gastric mucosa (and perhaps protective) is held by some authors based on contradictory results obtained in animal and human studies. A careful study of gastric mucosal morphology and its association with reflux is therefore indicated.

Normal pyloric function is difficult to define and appears to differ from other gastrointestinal sphincters. Pyloric dysfunction or removal allows for retrograde movement of duodenal contents which may adversely affect gastric mucosa, producing gastritis or gastric ulceration. The clinical significance of reflux and/or gastritis is unknown because symptomatic and asymptomatic patients may give comparable results.

MATERIALS AND METHODS

The study consisted of two parts and the subjects for each part were very different. Pyloric pressures were studied in young healthy volunteers, whereas bile reflux and gastritis were studied in symptomatic patients undergoing gastroscopy. Informed consent was obtained in all cases, and the study was approved by the Ethics Review Committee of the University of Alberta Hospital.

I. Pyloric Pressure Studies

Simultaneous pyloric pressure and skin to mucosal potential difference (PD) were measured in ten normal volunteers and one patient with benign gastric ulcer. The normals had no history of gastrointestinal complaints and had not undergone abdominal surgery. There were seven females and three males with an average age of 22 years. The gastric ulcer subject was a female aged 55 years. The ulcer was located high on the lesser curve, not associated with achlorhydria and proven to be benign.

A perfused catheter system was used. Several different tubes were tried before adopting the Arndorfer-McSteen esophageal motility tube (O.D. 6.3 mm). It compared favourably with tubes used by other investigators (Fisher[54], 1973; Kaye[78], 1976). There were adequate numbers of individual catheters built into the composite tube with convenient radio-opague markers and colour-coded connectors corresponding to each sidehole. However, the tube was essentially designed for esophageal motility studies and therefore several modifications were

necessary. First of all, the tube length from the triple-sidehole site to the tip was only five centimeters, making it difficult to adequately traverse the duodenogastric junction on a pull-through with the pressure-sensing openings while still retaining sufficient tubing in the duodenum to facilitate re-intubation. An additional five centimeter segment of identical tubing was, therefore, attached to the tip giving a tip-to-triple-sidehole length of ten centimeters. Secondly, to facilitate fluoroscopic monitoring during transpyloric duodenal intubation, three additional metallic markers were placed in the distal five centimeters of tubing. A latex balloon containing 1.5 cc of mercury was attached to the catheter tip. The central catheter which originally opened at the tip was opened through a new 1.2 mm sidehole situated two centimeters from the tip. The final tube after these modifications appeared as illustrated in Fig. 1.

Pyloric pressures were measured by perfusion of the catheter system using a low compliance pneumohydraulic infusion pump. Distilled water was infused at a rate of 0.25 cc per minute per pressure channel, and pressures were recorded on a Beckman R-411 Dynograph. A continuous record of respiration and movement artifact was also obtained.

The skin-to-mucosal electrical potential difference (PD) was recorded continuously by infusion of a conducting column (Ringer's lactate plus 40 mEq KCℓ/L) with a Harvard pump at a rate of 0.38 cc per minute. The PD was measured between the conducting column on a HP14240A monitoring electrode placed on skin in the left epigastrium. The Beckman R-411 Dynography served as a voltmeter and recorded directly

any PD change. One of the three openings at the 10 cm level served both functions as markers of PD change and intraluminal pressure.

The procedure followed can be outlined in chronological order. No premedication was given, and subjects were not permitted to smoke for two hours prior to the test. The subject was fasted for at least eight hours followed by per-oral gastric intubation with the motility tube. The tube was then positioned in the second or third part of the duodenum under fluoroscopic control. Once positioned in the duodenum, a basal static recording was obtained until Phase III of the inter-digestive myoelectric complex (IDMEC) could be seen, or for one hour, which ever came first. With the subject supine, a resting pull-through in one half centimeter increments was performed. Once the area of PD change had been traversed, the tube was re-inserted into the duodenum and its position confirmed fluoroscopically. Once re-stabilized, a stimulated pull-through was performed. This involved intraduodenal infusion of 0.1 N Hydrochloric acid through the most distal port with a Harvard pump at 7.6 cc/minutes. Five to ten minutes after the infusion was started, a second pull-through was performed in a similar manner. Acid infusion was continued during the stimulated pull-through to a maximum of 110 milliliters.

The site of PD change served as the major marker for identifying the pyloric region. Additional clues were obtained by noting that channel one (most proximal opening at 25 cm from tip) was generally at the lower esophageal sphincter when channels three, four and five (triple openings at 10 cm from tip) were at pylorus, or by comparing the wave forms and frequency of channel two (openings at 15 cm from tip)

with channels three, four, and five.

Resting and stimulated recordings were examined for any elevations of pressure above duodenal (zero reference) pressure. The height and length of each pressure peak were noted as well as its location relative to the site of PD change. Phasic contractions were not quantified.

II Duodenogastric Reflux

Duodenogastric reflux was assessed by two different methods on separate days. Forty patients underwent gastric fluid analysis, and eighteen of these cases also had scintigraphic examination.

A. Radionuclide Assessment

Radionuclide measurement of reflux was performed similar to the method outlined by Tolin et al[129] (1979) but with several differences. Subjects were fasted and placed supine under the Siemens large field of view gamma camera with Ops-Con on live data processor. An intravenous injection of 480 megabecquerel (mBq) ^{99m}Tc-dimethyl imminodiacetic acid (I.D.A.) was given followed by continuous imaging in 30 second frames. Patients were kept supine for the duration of the study. After one hour, a fatty meal was administered, followed in 30 minutes by ^{99m}Tc-sulfur colloid 111 mBq orally to outline the stomach. Similar methodology has been described by Shaffer et al[124], 1980. Analogue and digital data were stored on floppy discs. Activity time curves were generated by light-pen definition of anatomical regions and replaying of the floppy discs. In addition the analogue images were interpreted as reflecting or not reflecting duodenogastric reflux.

B. Gastric Fluid Analysis

The subject material for this study consisted of 40 symptomatic patients undergoing gastroscopy. Normal volunteers were not recruited. The indications for endoscopy were investigation of abdominal pain (75%) and esophageal complaints (25%). The principal diagnosis in these patients were: x-ray and endoscopy negative dyspepsia (50%), esophageal motility disorders and gastroesophageal reflux (27.5%), gallstones (15%), and miscellaneous (7.5%), as outlined in Table 1. Excluded from the study were patients with active ulcer, erosions, recent bleeding, marked pyloric deformity, and previous gastric surgery.

Patients were fasted for 12 hours and premedication was withheld until immediately prior to gastroscopy at which time atropine 0.6 mg and diazepam were administered intravenously. The dosage of diazepam varied and was titrated to an acceptable level of drowsiness. The patient was then positioned on the left side and the pharynx anesthetized with topical lidocaine spray. The flexible fiberoptic gastroscope (A.C.M.I. or Olympus) was introduced per os and the esophagus examined. As soon as possible after entering the proximal stomach with the scope, complete aspiration of the gastric content was performed. Small amounts of air were introduced as necessary to ensure complete evacuation of gastric liquid. Once gastric aspiration was complete, a sequential examination of stomach and duodenum was done to rule out active ulceration, erosion, or marked pyloroduodenal deformity. In suitable cases, the aspirated fluid was sent for analysis and gastric biopsies performed.

C. Biochemical Methods in Brief

The aspirated gastric content was collected on ice and as soon as possible screened for the presence of bilirubin. The ictetest (Ames) was performed by adding a drop of water after placing a sample and the test tablet onto filter paper. If a blue colour was observed the test was considered positive. The volume of the specimen in milliliters was recorded, as well as the pH, which was determined with either pH paper or on a pH meter.

Total phospholipid concentration was determined colourimetrically after digesting the sample with sulfuric acid, adding ammonium molybdate plus amino-naphthyl-sulfuric acid (ANSA) to measure inorganic phosphorus. The specimen was then examined for blue colouration at a wavelength of 675 mm.

Cholesterol concentration in the sample was determined by the discrete analyzer using a specific enzyme method (Abbott) or colourimetrically (Liebermann-Meffert reaction).

Lecithin and lysolecithin were determined semiquantitatively by thin layer chromatography and recorded as 0, 1+, 2+, ..., 5+.

Fractionation of bile into primary (cholic and chenodeoxycholic) and secondary bile acids (deoxycholic and lithocholic) was done by gas chromatography as previously described by McDougall[98, 99]. A detailed discussion of the biochemical methods is given in the appendix.

III Morphology

Gastric mucosal biopsies were taken with the A.C.M.1. #7035A Teflon coated spike forceps from 11 specific sites as illustrated

in Fig. 2. Eight biopsies were taken from the antrum: four from the lesser curvature beginning at the incisura angularis and at approximately equally distant segments distally to the pylorus; and similarly, four from the greater curvature beginning at a point opposite the incisura in a distal fashion to the pylorus. Three biopsies were obtained from the body and fundus of the stomach. One was taken from the lesser curvature midway between the gastro-esophageal junction and the incisura. Two biopsies were obtained from the greater curvature, one high in the body approximately at the junction between fundus and body, and another from a site midway between the previous biopsy and the area where the folds tapered off into the antrum.

Each biopsy was oriented mucosal side up on monofilament plastic mesh and fixed in Bouin's solution (3 L. Sat. Acqueous Picric, 1 L. 38% Formalin, 40 c.c. Glycyl Acetic) for approximately four hours. Biopsies were processed as previously described for small bowel biopsies (Perera, Weinstein and Rubin[110], 1975). From the central core of each specimen approximately 60 consecutive sections were prepared and stained with hematoxylin and eosin. In addition, another 15 serial sections were stained with Alcian blue at pH 2.5 to help detect small foci of intestinal metaplasia.

The biopsies were evaluated by Dr. Weinstein without prior knowledge of the clinical or endoscopic findings.

IV Analysis of Results

A. Pyloric Manometry

The pyloric region was identified on the graphs by the site of abrupt PD change on pull-through. Furthermore, the appearance of LES on the most proximal tracing corresponded roughly to a pyloric location of the triple sideholes (a lesser-curve length of 15 cm) and this proved helpful in cases where PD change was less obvious. Any pressure elevations above baseline gastric pressure were noted and quantitated (amplitude and duration). Pressure fluctuations with respiration occurred, and the assessed value was halfway between peak inspiratory and trough expiratory pressure. Basal and post-acid infusion records were processed identically and the values compared.

B. Radionuclide Assessment of Reflux

The analogue images were compared with the corresponding barium swallow when available to better define the upper gastrointestinal anatomy. An appropriate "window" was then chosen to represent the gastric body and fundus, and an attempt made to determine visually the presence of duodenogastric reflux. Activity time curves were generated by light-pen definition of these anatomical regions and the floppy discs replayed. In this way the time of reflux as well as the quantity could be noted.

C. Gastric Content Analysis

Gastric fluid was tested for bilirubin soon after aspiration, and later processed in batches for total bile acid, cholesterol, total phospholipid concentrations, bile acid fractionation and presence of

lecithin/lysolecithin. Accuracy of results was confirmed by repetition of biochemical procedures on several samples, as well as by using several different methods to measure one parameter in a single sample (e.g. Cholesterol).

The total bile acid concentration was found to be more reliable than the ictetest and therefore was chosen as the better criterion for the presence of reflux in borderline cases. The amount of bile refluxed was calculated by multiplying the concentration of total bile acids by the volume of fluid aspirated from the stomach.

D. Morphology

The grading system was similar in both antral gland (pyloric gland) and fundal gland (oxyntic) biopsies. Each biopsy was classified as antral, fundal or transitional. Biopsies were classified as transitional if there was a combination of both clear-staining (mucous type) antral glands and parietal and *chief* cells. Antral gland biopsies that contained only isolated parietal cells, a not uncommon finding (Kimura[84], 1972), were still graded as antral gland type and not transitional.

In abnormal biopsies, individual morphologic features were graded according to severity of involvement: surface epithelium, neck changes, inflammatory infiltrate, round cells (lymphocytes and plasma cells), polymorphonuclear leukocytes or both. The presence or absence of intestinal metaplasia was noted and an approximation of severity was made. When the inflammatory infiltrate or intestinal metaplasia involved the full depth of the mucosa in a portion or all of the biopsy, the term "full thickness" was used. In antral gland biopsies, apparent thinning

of the glandular layer without inflammation was not interpreted as "atrophy" because of normal variations in antral gland depth. On the other hand, in fundal gland biopsies ther term "atrophy" was used in relation to biopsies where there was little or no inflammation and obvious presence of transitional gland elements or outright antral-gland-appearing mucosa.

In order to be considered interpretable for this study the biopsy had to be deep enough to contain the gland layer (3% of antral biopsies and 25% of fundal biopsies did not include muscularis mucosa). For computer analysis of various abnormalities severity grades were assigned numerical values. Each biopsy was scored separately and mean values calculated by averaging the numerical scores for that anatomic region.

RESULTS

I. Pyloric Pressure Studies

Basal recordings were obtained in 10 normals, 3 males and 7 females, of average age 22 years. The pyloric region was identifiable in 7 subjects by a PD change. In 3 cases this was not possible (no PD change in two and eratic PD oscillations in one) and their recordings were excluded from the analysis. Reintubation of the duodenum failed in one subject, leaving six stimulated recordings for analysis. The gastric ulcer patient records were examined separately. LES was readily identifiable in all subjects, as was phase III of the I.D.M.E.C., seen in 5 cases.

A typical record is illustrated in Fig. 3. Channel 7 shows PD change and channel 1 marks LES. Channel 5 shows a pressure peak with a height of 10 cm H_2O, a length of 2 cm and location just preceding PD change. This could indeed represent the pylorus. However, there are no corresponding peaks in channels 3 and 4 with pressure-sensitive openings at the same axial level as channel 5. Furthermore, channel 5 shows a second pressure peak beginning .5 cm proximal to the site of PD change with a height of 5 cm H_2O and length of 3 cm. This could likewise represent the pylorus. Which one is it?

The dilemma is also demonstrated by another example (Fig. 4). The I.D.M.E.C. phase III activity is seen just before starting the resting pull-through. Multiple distinct pressure peaks are found with no apparent relationship across channels or the site of PD change.

The results for the six normals at rest and six normals after acid infusion are graphically portrayed in Fig. 5. The records from the gastric ulcer patient are illustrated in Fig. 6. A total of 34 recordings were examined and all failed to show pressure peaks which were both localized to the area of PD change and common to all three channels at the appropriate level. Ironically, the subject most nearly fulfilling those criteria was the gastric ulcer patient after acid infusion.

II Duodenogastric Reflux

A. Radionuclide Studies

Analogue evidence of reflux was present in 4 of the 16 cases available for analysis and three of these were positive on gastric analysis. The other 12 cases were considered negative, although six of these proved to be positive on gastric analysis. The mean age of ^{99}Tc refluxers was 46.25 years and of non-refluxers was 45.17 years. The sex distribution, personal habits and symptom scores of the two groups were comparable. Gastritis scores did not vary significantly between these two groups, as portrayed in Table 16.

B. Gastric Content Analysis

a. Patient Population

Forty patients were included in this study of bile reflux and gastritis. All were symptomatic and undergoing gastroscopy. There were twenty-five females (mean age 45 years) and fifteen males (mean age 48 years). The overall mean age was 46 years with a range of 21 to 87 years. Eight patients had undergone previous cholecystectomy,

and an additional six patients were found to have gallstones. The clinical diagnostic categories were: esophageal complaints, 11 cases (achalasia - 3; gastroesophageal reflux - 6; diffuse esophageal spasm - 2); dyspepsia of undetermined etiology (20 cases); gallstones (6 cases), and miscellaneous (3 cases: angina pectoris; investigation of anemia; and chronic pancreatitis). Eighteen patients were cigarette smokers, fifteen drank alcohol (none heavily) and thirty-one drank coffee. Total symptom scores ranged from zero to twenty-two with a mean score of 11.5 ± 5.24 points. Fifteen complained of anorexia and weight loss. Twenty-four experienced symptomatic improvement with antacids. Other medications were noted but not integrated in the study because of the heterogeneity of type and dosage. Excluded from the study were patients with recent gastrointestinal hemorrhage, acute erosions, active ulceration, and those with a history of previous gastric surgery.

b. Biochemical Studies

The presence or absence of visual gross bile staining of the specimen was recorded for 25 of the 40 samples. The concentration of total bile acids (TBA) was invariably elevated if bile staining was evident grossly. Lack of bile staining was indicative of low TBA concentrations.

The ictetest proved to be unreliable at low pH for TBA concentrations below 1 m Molar. The lowest TBA concentration giving a positive result on ictetest was 0.40 m M/L at pH 2.5, and therefore this concentration was chosen as the criterion for the presence of bile reflux.

Discrepancies occurred in four cases, i.e. - ictetest was negative, but TBA concentration was .4 m M/L or greater, and these cases were grouped with the refluxers.

Case # 32	TBA = 0.40 m M/L	pH 6.5
Case # 36	TBA = 0.44	pH 2.0
Case # 27	TBA = 0.56	pH 2.0
Case # 40	TBA = 0.86	pH 1.9

The total number of bile refluxers was 18 of 40 cases (45%) (14 were ictetest positive, 4 were ictetest negative, but all had TBA concentrations 0.4 m M/L or greater). Table 2 shows the TBA concentrations, pH and volume and ictetest results for each case. NSO in 6 cases, none with visual bile and all ictetest negative. The distribution of TBA concentrations varied from zero to 9.0 mMol/litre.

Cholesterol, total phospholipids, and lecithin/lysolecithin estimations were carried out on refluxers only, and the values are shown in Table 3. Bile acid fractions are displayed in Table 4 giving their concentrations as well as percentage of the total quantity.

III Morphology

Multiple gastric mucosal biopsies were performed in 40 patients. Out of a possible 440 biopsies, 424 (96.4%) were available for analysis; 3.6% of biopsies were too shallow to permit satisfactory histologic evaluation, or were lost or damaged in processing. Biopsies which showed surface and glandular detail but lacked enough depth to include muscularis mucosae were considered adequate for analysis: this circum-

stance arose in 3% of antral biopsies and in 25% of fundal biopsies. Transitional mucosal type was present in 52 (16%) biopsies taken from the endoscopic antrum, and in 11 (9%) biopsies from the endoscopic fundus. Fundal mucosal type was found in 42 (13%) biopsies from the endoscopic antrum. Only three (2%) biopsies from the endoscopic fundus were called antral mucosal type suggesting "antralization" of the fundus.

Atrophic changes were sought in fundal biopsies only and were found in eight patients (16 biopsies; 13%). Intestinal metaplasia was present in 18 patients (53 biopsies; 12%) and varied considerably in severity.

The histologic data is presented in numerical form as gastritis scores in Tables 5(a - e). The total gastritis score per biopsy was calculated by summation of individual scores for each of five parameters (surface change, round cell infiltrate, depth, polymorphonuclear leukocytes, and glandular neck changes) and is presented in Table 6. Mean gastritis scores were calculated for each parameter by adding the appropriate numerical value and dividing by the number of contributory biopsies (average value). The mean values for various anatomical regions are presented in Table 7(a - d). Table 8 is derived by adding individual mean scores for the five parameters thus producing the total mean gastritis scores for various anatomic divisions. All biopsies from the endoscopic antrum (numbers 1 - 8) which showed fundic mucosal type were excluded from analysis. Tables 5, 6, 7, 8 outline the basic morphologic data which provided the basis for the following correlations.

IV Correlative Data

A. Gastritis and Age

Patients were grouped according to gastritis scores for various anatomic areas and, as shown in Table 9, the groups compared with respect to age. In general, it was found that increasing gastritic score was associated with increasing age of patients. Sequential group comparisons do not consistently attain statistical significance. However, comparing patient ages in groups of gastritis scores less than four versus scores greater than four for each anatomic region shows a highly significantly difference ($p < .001$). Thus, the patients with greater morphologic changes are significantly older than those with lesser gastritis.

A clearer correlation can be found by examining the problem inversely - i.e. grouping patients according to age and comparing patients scores. Table 10 demonstrates the significantly increased gastritis with increasing age. Each individual component was found to increase in parallel with the total gastritis score when comparing different age groups as illustrated in Figure 7. The total mean gastritis score was, therefore, representative of each individual histologic parameter.

Atrophic changes were identified in eight patients, mean age 61.8 years versus all other patients mean age 42.0 years ($p < .001$). Intestinal metaplasia was present in [illegible] patients, mean age 52.0 years (mild in 10 patients, mean age 40.1 years; extensive in 8 patients, mean age 66.8 years) versus 22 patients without metaplasia of mean age 41.3 years ($p < .001$).

B. Gastritis and Reflux

There were 18 patients with duodenogastric reflux as measured by a total bile acid concentration of 0.40 m M/L or greater in the gastric fluid. Table 11(a) demonstrates significantly increased gastritis scores in refluxers compared with non-refluxers. Similarly the *amount* of bile aspirated from the stomach correlates significantly with increased gastritis scores (Table 12) for total and individual means. Table 11(b) gives further descriptive data comparing and contrasting refluxers with non-refluxers of bile.

A more detailed analysis of gastritis as it related to total bile acid *concentration* is given in Table 13, which suggests that the best correlation is found in fundic mucosa. The individual mean gastritis scores again appear to parallel the total mean scores.

An inverse analysis of the problem was again performed. Using the same morphologic groupings as for age analysis (Table 9), the severity of reflux with respect to total bile acid concentration amount of total bile acid and percentage of cases per group having positive ictetest results was correlated with increasing severity of gastritis (see Table 14). It becomes apparent that a greater percentage of patients with severe gastritis have bile present in the stomach. The concentration of bile, however, was extremely variable, thereby introducing a very large standard deviation, and failing to attain statistical significance. Table 15 shows individual mean gastritis scores and the corresponding reflux parameters. Again the percentage of cases refluxing correlates better with gastritis than the amount

or concentration of bile acids.

Using radionuclide assessment of reflux in 16 cases, it was found that there was no significant difference in morphology between refluxers and non-refluxers (see Table 16).

The presence and relative amounts of lysolecithin in the gastric fluid proved of no importance as a determinant of gastritis, except perhaps in fundic mucosa (see Table 17).

C. Duodenogastric Reflux and Age

The mean age of refluxers (53.0 years) was significantly different from non-refluxers (40.4 years). Table 18 shows age groupings and corresponding degrees of reflux. All patients aged 60 years and over were found to reflux bile whereas only 20% of patients aged 20 to 29 years refluxed. The *concentration* of bile acids showed a lesser correlation with age.

Conversely, the age of patients grouped according to concentration or amount of bile acids present increased significantly (see Tables 19, 20).

The mean age of refluxers with radionuclide testing was 46.3 years compared with 45.2 years for non-refluxers, showing no significant difference.

D. Other Factors Influencing Gastritis and Reflux

a. Presence of Gallbladder Disease

Eight patients had undergone previous cholecystectomy and an additional six patients were found to have gallstones giving a total

of 14 patients with gallbladder disease. Bile reflux was present in 57% of these patients compared to only 38.5% of patients free of gallbladder disease (statistically insignificant, $x^2 = 1.28$). Moreover, using Student's t test for two means, the concentrations of total bile acids and amounts of bile acids were significantly increased in the diseased group (see Table 21). Also contained in this table are the corresponding gastritis scores of these two groups of patients, again showing a significantly increased gastritis in gallstone patients, especially for fundic mucosa.

b. Sex

The study included 25 females of average age 44.9 years, and 15 males of average age 48.1 years. Reflux was present in 52% of females, but only 33% of males. This difference proved statistically insignificant ($x^2 = 1.32$). The *concentration* of total bile acids in females was, however, significantly higher in females ($t = 12.97$; $p < .01$). These figures as well as gastritis score for males and females are presented in Table 22. Female patients exhibited both increased reflux and gastritis compared to males.

E. Matched Groups: Gastritis in Refluxers Versus Non-Refluxers

Because of the significant influence of age, sex and gallbladder disease on gastritis scores, as demonstrated above, it became necessary to control these factors in order to obtain a clearer understanding of the role played by refluxed duodenal content. Individual cards were constructed for each patient containing only a number, the age, sex and gallbladder disease status. The cards were grouped as refluxers and

non-refluxers and matched as closely as possible. Because all older patients refluxed, these could not be matched, therby reducing the group size to thirteen patients each. Table 23 portrays the matched groups' results, showing a significantly higher gastritis score for refluxers compared to non-refluxers.

These same groups of matched patients were compared with respect to multiple additional factors, none of which showed significant differences. The factors examined were: total symptom score, individual symptom scores, anorexia, weight loss, personal habits (smoking, coffee and alcohol consumption), presence of post-prandial pain, pain relief with antacids, and evidence of gastric atrophy or intestinal metoplasia.

F. Symptoms

The presence and severity of eight symptoms was noted and numerical symptom scores assigned. The average symptom score was 11.5, with a range of zero to twenty-two. No significant differences were noted when comparing these scores for refluxers versus non-refluxers (Table 24) or for types or severity of gastritis (Table 25). Inversely, the severity of symptoms did not correlate with total mean gastritis or individual components of gastritis (Table 26).

DISCUSSION

I. Pyloric Pressure

The perfused catheter system for measuring intraluminal pressures has been used extensively experimentally and clinically, especially for studying the esophagus and the rectum. Similar methods were used to attempt to demonstrate consistent manometric evidence for a pyloric sphincter in humans, but these efforts proved fruitless in our hands. Other workers report variable success, ranging from complete inability to delineate a pylorus[78] to attributing physiologic significance to apparent differences in observed pressures.[54, 55, 131] Our recordings were generally of good quality and invariably demonstrated the LES (lower esophageal sphincter) which is of greater magnitude. The pyloric region did not show a significant rise in pressure at rest. In fact, even with acid infusion there was no obvious pylorus. Potential difference measurements proved to be a useful method of identifying the area of mucosal change at the pylorus. The tube size was larger than that used by Kaye and by Fisher (6.3 vs 5.3 mm O.D.). This factor should have made it easier, if anything, to measure a pylorus because it would lie closer to the mucosa. Positional change might have contributed to our lack of success, as our subjects were supine, but those of Fisher[54], and Valenzuela[132] were in a right lateral decubitus posture. Kaye[78] argued that the postural change could artifactually demonstrate a "pylorus".

Manometric asymetry if measured circumferentially has been described for the lower esophageal sphincter (Winans[140]) and may well be present for the pylorus. This factor would be expected to have minimal influence

on multiple recordings, especially with the three spaced openings at the same axial level.

No particular significance can be attributed to the one case of gastric ulcer but she appeared to demonstrate a pylorus and to perhaps respond to acid infusion.

Consistency in interpretation of manometric records of pyloric pressures is lacking. Observer bias could play a major role because of lack of standard criteria. For example, Fisher, et al[54] averaged the pressure elevations with pylorus to arrive at a mean pressure. Thus pressure elevations were not considered essential in all recordings. Furthermore, no mention is made of similar pressure elevations occurring in the vicinity of the pylorus thus creating ambiguity. Presumably such pressure fluctuations were ignored by the authors while attributing physiologic significance to specific peaks considered to represent the pyloric sphincter. Our experience would suggest that additional pressure peaks at the duodenogastric junction are the rule rather than the exception.

Kaye and coworkers[78] used rather rigid creteria which are applied to similar manometric recordings but produce diametrically opposed conclusions concerning the pylorus. These workers stipulated that pressure elevations must occur simultaneously in all recording channels at the pylorus and that a zero pressure is one channel should not be averaged with other values. Instead, a zero value in the face of appropriate pressure changes in the other two recordings was interpreted as nullifying the presence of a pylorus. These criteria may prove

to be too stringent when applied to a signal with very low normal pressures, but they point out the need for the establishment of uniformity of interpretation of data.

Perhaps a combination of positional manipulation (Rt. lat. decubitus) and a potent specific stimulant of pyloric activity would allow consistent manometric identification of the pyloric ring. The element of specificity is stressed because it would allow differentiation of pyloric pressure fluctuations from various other pressure changes in the vicinity of the pylorus. Once this technical advance is accomplished it would be possible to apply manometric methods in a meaningful way to the study of pyloric function and dysfunction in health and disease.

II Duodenogastric Reflux

Aspiration of gastric fluid at gastroscopy has the advantage of visualizing the pool directly and ensuring complete emptying. However, the disadvantages are many. As with other methods, it can only determine the presence of reflux over a brief time period without knowledge of the remainder of time. Patients are premedicated and placed on their side, both factors possibly influencing the presence of reflux. Certainly, any difficulty in introducing the gastroscope would lead to retching and resultant reflux. It is surprising that gastric aspiration proved useful in categorizing patients.

The incidence of 45% bile reflux compares favourably with other studies.(10, 14, 21, 26, 27, 57, 71, 86, 91) Increased reflux with age was found and would be anticipated in support of the postulated role in gastritis. The concentrations and amount of bile refluxed

varied greatly between patients. However, the total quantity available for fractionation into individual components was generally too small. The ictetest accuracy could have been improved by first clearing the samples with sodium hydroxide (Keighley[79]), but this step was omitted.

Radionuclide testing for reflux was difficult to evaluate. Perhaps the procedure was abandoned too early, and only sixteen patients were tested. The four cases that refluxed were similar to the twelve that did not when comparing age, habits, gastritis or bile concentration. It was difficult to differentiate between true reflux into stomach and artifact from high counts in the overlying small bowel at the ligament of Treitz. Both methods of assessing reflux should be validated by comparison to an absolute standard, but none is available. Repetitive sampling might have proved helpful in confirming or negating the presence and extent of reflux but this was not done.

III Gastritis

The flexible gastroscope makes it possible to map out gastric mucosal morphology by fairly accurate sampling from multiple sites. Gastritis was found to increase with age as expected from previous work[2, 81, 84, 87]. In spite of criticisms regarding the accuracy of gastric aspiration as an indication of bile reflux, a significant positive correlation of reflux with gastritis was demonstrated. This correlation persisted after controlling for age, sex and presence of gallbladder disease, factors which were shown to influence gastritis scores. *In vitro* and *in vivo* experiments have demonstrated gastric mucosal changes secondary to exposure to bile or duodenal contents[35, 36, 40, 88, 89] but even this data is not undisputed[24, 110]. A clinical study therefore, is unlikely to resolve the argument.

Radiologic and gastroscopic negative dyspepsia is often diagnosed as "gastritis" without histologic evidence. Such practice is wrong on two counts. First, gastritis is a histologic diagnosis which does not correlate with endoscopic appearance. Secondly, the clinical diagnosis of "gastritis" implies that mucosal changes are responsible for symptoms. Our study suggests that no such relationship exists. Patients with severe symptoms had similar gastritis scores to relatively asymptomatic ones. On the other hand, patients with severe gastritis sometimes had few symptoms.

The exclusion of certain patients from the study may have selectively influenced the results. Perhaps patients with acute gastric erosions, for example, would have a different anatomic distribution of gastritis (antral vs fundic) or possibly an atypical individual component of gastritis (polymorphs or surface change). This study is unable to exclude such a possibility.

IV Summary

A pyloric sphincter could not be demonstrated manometrically in ten normal subjects and, therefore, the procedure was not carried out in the study group.

Bile reflux occurred in eighteen of forty symptomatic unoperated cases undergoing gastroscopy for various reasons. Those patients having gastric bile showed significantly increased gastritis. This correlation persisted after controlling for age, sex and presence of gallbladder disease, each of which also influenced gastritis scores.

No relationship could be demonstrated between symptoms and either bile reflux or gastritis.

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APPENDIX A

PHOSPHOLIPID ANALYSIS

1. 1 ml specimen was added drop by drop to 22 ml $CHCl_3$ - CH_3OH (2:1) on the vortex and left to stand in excess of five minutes.
2. The tube was stoppered, shaken for 30 seconds, brought to 25 ml by adding more $CHCl_3$ - CH_3OH, and left to stand for an additional five minutes.
3. 5 ml dilute H_2SO_4 (1 ml concentrated H_2SO_4 to 2 liters dejonized water) was added, the tube inverted 10 times, and left standing for 10 minutes.
4. Centrifugation at 2,000 RPM for 15 minutes separated the lower chloroform phase containing the lipids. Phosphorus was then liberated from the lipids and reacted with acid molybdate solution to form phosphomolybdic acid which was reduced by aminonapthol-sulfonic acid to yield a blue colour by the following method:
   1. 5 ml extract was evaporated to dryness, 2.5 ml of 5N H_2SO_4 added, and the mixture slow boiled.
   2. After a black or brown colour change occurred, one drop of 30% H_2O_2 was added and heating continued for at least 10 minutes until the contents became colourless. If unsuccessful this step was repeated.
   3. A standard was prepared by transferring 0.5 ml of phosphate

standard (0.08 mg phosphorus per ml) to a digestion tube and adding 2.5 ml of 5N H_2SO_4. 2.5 ml of 5N H_2SO_4 was used as a blank. The same amount of H_2O_2 as used in step 2 was added, and the tubes boiled for 10 minutes.

4. Contents were diluted with a few ml deionized water, cooled to room temperature, and transferred to 25 ml volumetric flasks with repeated washings so the flask was half full.

5. 2.5 ml ammonium molybdate solution (2.5% w/v) and 1 ml aminonapthol-sulfonic acid reagent were added. Contents were diluted to the 25 ml mark with deionized water, mixed, and allowed to stand for five minutes.

6. Measurements of optical density were made with the Unicam S.P. 1800 spectrophotometer at 675 nm.

7. Calculations:

$$\text{mg\% phospholipid} = \frac{\text{O.D. unknown}}{\text{O.D. standard}} \times 0.04 \times 18 \times 100 \times .25$$

Millimolar concentration was found by employing the conversion factor:

1 mM phospholipid = 793 mg/l.

APPENDIX B

TOTAL BILE ACIDS METHOD

Reagents were:

1. Buffer, 0.1 M sodium pyrophosphate.
2. Hydrazine sulphate 1.0 M (3.4 ml 95% hydrazine plus 1.5 ml concentrated H_2SO_4, q.s. to 100 ml with deionized water).
3. NAD, 6.8 mM.
4. Enzyme prepared from Pseudomonas testosteroni (Sigma, Type 1).

Procedure was carried out as per Table 12. All tubes were then incubated at 37°C for 60 minutes. Spectrophotometric determinations were made at 340 nm. A graph was constructed by plotting mM concentration of chenodeoxycholic acid standards against optical density and values obtained for the bile samples from their optical densities.

TABLE 27

Bile Salt Analysis Procedure: Assay

	Blank(ml)	Test(ml)	CDCA Standards ml		
Buffer	2.0	2.0	2.0	2.0	2.0
Hydrazine	1.0	1.0	1.0	1.0	1.0
NAD	0.5	0.5	0.5	0.5	0.5
Bile	0.003	0.003	–	–	–
Enzyme	–	0.025	0.025	0.025	0.025
Boiled Enzyme	0.025	–	–	–	–
Chenodeoxycholate Acid	–	–	0.01	0.03	0.05

APPENDIX C

BILE ACID FRACTIONATION (GLC)

Preparation of Samples (To be done in Duplicate)

Standards

1. To three 15 ml capped test tubes add 50, 100, and 200 µl of an ethanolic solution containing 0.5 mg/ml of lithocholic, deoxycholic, chenodeoxycholic and cholic acids.
2. Similarly add 50, 100, and 200 µl of a 0.4 mg/ml methanolic solution of cholesterol.
3. Add 100 µl of a 2 mg/ml ethanolic solution of 7-ketodeoxycholic acid as an internal standard.

Conjugated Standards

1. To a single capped test tube add 100 µl each of a 2 mg/ml solution of glycocholic and taurochenodeoxycholic acids.
2. Evaporate to dryness in a 60°C water bath, blowing with nitrogen.
3. Add [illegible] acetate buffer pH 5.6, 0.1 M.

Specimens - Recoveries

1. Dilute specimen by adding 100 µl to 3 ml acetate buffer.
2. Add 1 ml dilute bile to three capped test tubes #1, 2, and 3.
3. Add 100 µl each of the 2 mg/ml ethanolic solutions of glycocholic and taurochenodeoxycholic acids to tube #2.

4. Add 100 µl cholesterol t

Specimens - Additional

Prepare dilute bile as above and add 1 ml to a single capped test tube. Repeat for as many samples as necessary.

Hydrolysis

Preparation of Enzyme

1. For each specimen plus the conjugated standards, grind 10 mg Clostridium welchii acetone powder (containing cholylglycine hydrolase) with 10 mg alumina in a mortar. Add 4 mg disodium EDTA and dissolve in 1.5 ml acetate buffer. Add 0.15 ml of a 0.1 M solution of β-mercaptoethanol. Centrifuge at 2000 RPM for a few minutes, and retain supernatant.
2. Add 1.5 ml enzyme solution to tubes containing specimens and conjugated standards.
3. React in a 37°C water bath for 4 - 5 hours.
4. Prior to extraction add 200 µl of the 0.5 mg/ml solution of free bile acids to specimen recovery tube #3.

Extraction of Free Bile Acids

1. Acidify to pH 1 by adding 1 ml 6N-HCl.
2. Add 5 ml ether and run on shaker for 5 minutes. Centrifuge at 2000 RPM for one minute, and pipette supernatant into a capped test tube to which has been added 100 µl of a 2 mg/ml solution of 7-ketodeoxycho acid. Repeat extraction three additional times.
3. Evaporate to dryness in 40°C water bath, blowing with nitrogen.

Methylation

To each test tube (standards and tests) add 1 ml of a 5:1 mixture of ether methanol.

Preparation of Diazomethane

1. Stopper two 50 ml test tubes and connect with glass tubing projecting 2 cm into the top of the reaction tube and projecting to the bottom of the collection tube. A second piece of tubing (N_2 inlet) goes through the stopper to the bottom of the reaction tube, and a third piece (N_2 outlet) projects 2 cm through the stopper of the collection tube.
2. Distillation apparatus is placed in a well ventilated fume hood and the collection tube is immersed in a beaker containing ice.
3. Add 15 ml ether to the collecting tube and 7 ml ether to the reaction tube.
4. Add 0.5 gm Diazold and 2 ml of alcoholic KOH (1.5 gm KOH/30 ml ethanol). Stopper tubes and bubble N_2 through, until reaction tube becomes whitish (20 minutes).
5. Add 1.5 ml diazomethane and react (10 minutes) until there is a persistent light yellow colour. Tightly cap tubes.
6. Place in a 60°C water bath and evaporate to dryness by blowing with N_2.

Preparation of TFA Derivatives

1. Add 0.3 ml trifluroacetic anhydride and tightly cap tubes. React at 37°C in a water bath for 30 minutes. Evaporate to dryness in a 60°C water bath by blowing with nitrogen.
2. Dissolve residue in 200 ml acetonitrile.

Gas-liquid Chromatography

Preparation of a Column

1. Silanization

   a. A glass column 1/8" x 3 ft. is washed with 50 ml of DIW, methanol, acetone, chloroform, and toluene, then silanized under a vacuum with 80 ml 2% dimethylchlorosilane in toluene (DMCS).

   b. Rinse with 200 ml methanol and leave under vacuum until dry, 6 hours.

   c. Glass wool. Soak in 1/200 photoflo/H_2O for three hours, blot dry, and dry at room temperature.

2. Packing

   a. Place a small plug of glass wool in the outlet and under vacuum pour small amounts of QF-1 (1.5% on chromasorb W AW-DMCS 80 - 100 mesh) into the inlet via funnel and tubing. Pack by tapping column with a pencil covered with rubber tubing. Fill to 5 cm below inlet.

   b. Protect inlet with a small plug of sialinized glass wool.

   c. Keep on vacuum overnight.

3. Column Conditioning

   a. Condition at 240°C (QF-1 temperature limit 250°) for a minimum of 48 hours, with the outlet disconnected and the carrier gas flowing at about half normal rate.

Analysis Conditions

Injector 280°C

Manifold 290°

Column 200° x 1 minute, increase by 16° per minute to 230°

Nitrogen 50 ml/min

Inject 1 µl samples.

Results - Calculations

1. Peaks from the four free bile acid standards will allow construction of a standard graph for each bile acid if desired. They can also be used to program an instrument such as the Hewlett-Packard 5830A GC to calculate the amounts of the individual bile acids in a sample.
2. Percent recovery: extraction can be determined for free bile acids and cholesterol from recovery specimens #1 and #3 amounts, i.e.,

$$\frac{\text{Bile + standard (\#3)} - \text{Bile (\#1)}}{\text{standard}} \times 100$$

3. Percent recovery: hydrolysis can similarly be determined using the results from the conjugated standard hydrolysis and the results from recovery specimens #1 and #2, i.e.,

$$\frac{\text{Bile + conjugated standard (\#2)} - \text{Bile (\#1)}}{\text{conjugated standard}} \times 100$$

4. If percent recoveries are acceptable, additional specimen results may be used without further verification if duplicates agree.

TABLE 1: PATIENT POPULATION

Diagnostic Categories		No. of Patients
Esophageal Complaints		11
- achalasia	3	
- G-E Reflux	6	
- diffuse Spasm	2	
Dyspepsia		20
- duodenitis	4	
- "gastritis"	5	
- unknown	11	
Gallstones		6
Miscellaneous		3
- chronic pancreatitis	1	
- anemia	1	
- angina p[redacted]	1	
Total Number of Patients		40

TABLE 2: REFLUX DATA I

Case No.	Volume (ml)	pH	Ictotest	Concentrations Total Bile Acids (mM·1/L)	Amount Total Bile Acids (µM)
1	21	1	–	.11	2.3
2	105	1	–	.07	7.4
3	0	–	–	–	0
4	35	3.8	+	1.36	47.6
5	11	1.7	–	.1	1.1
6	42	1	+	1.08	45.4
7	24	3.5	–	.07	1.7
8	11	6.5	+	1.67	18.0
9	25	1.8	–	.12	3.0
10	22	3.5	–	.08	1.8
11	21	2.4	+	.6	12.6
12	28	5.6	–	–	–
13	30	2	–	.12	3.6
14	35	2.5	+	.4	14.0
15	13	3	–	–	–
16	10	4	–	–	–
17	7	6	–	.13	9.1
18	8	7	–	–	–
19	20	1.8	–	.07	1.4
20	29	5.8	+	9.0	261.0
21	10	1.5	–	–	–
22	15	7.5	+	.64	9.6
23	23	3.5	–	.07	1.61
24	12	4	–	.12	1.44
25	19	3	–	.08	1.52
26	17	4.5	+	4.68	79.6
27	25	2	+*	.56	14.0
28	28	3.4	–	.16	4.48
29	32	3	–	.25	8.0
30	8	7	+	.5	4.0
31	18	3	+	.6	10.8
32	47	6.5	+*	.40	17.9
33	27	2.5	+	1.12	30.24
34	88	7.8	+	8.28	728.6
35	15	3	+	6.32	94.8
36	45	2	+*	.44	19.8
37	54	4.5	–	.14	7.5
38	29	8.5	+	4.08	118.3
39	4	3	–	.09	.36
40	23	1.9	+	.87	20.0

* negative ictetest changed because of concentration TBA

TABLE 3: REFLUX DATA II

Case No.	Cholesterol (mM/L)	Total Phospholipids (mM/L)	Lecithin	Lysolecithin
4	.21	[illegible]	2+	1+
6	.05	[illegible]	2+	0
8	.41	[illegible]	0	1+
11	.10	[illegible]	TR	0
14	.18	.23	1+	0
20	.72	3.13	0	5+
22	.18	.13	2+	Tr
26	.88	.94	4+	4+
30	.18	.20	0	0
31	.13	.21	Tr	0
32	-	.36	0	0
33	.13	.73	2+	Tr
34	.80	1.28	4+	4+
35	.36	.54	4+	2+
38	1.01	0.57	3+	3+

TABLE 4: BILE ACID FRACTIONATION

Case No.	Lithocholic Acid mM/L	%	Deoxycholic Acid mM/L	%	Chenodeoxycholic Acid mM/L	%	Cholic Acid mM/L	%
4	.03	16.5	.11	6.4	.13	23.4	.20	42.6
6	.06	9.1	.05	7.6	.28	42.4	.27	40.9
8	.09	7.5	.22	18.3	.64	53.3	.25	20.8
11	0	0	.03	18.3	.09	56.3	.04	25
14	0	0	.06	28.6	.06	28.6	.09	42.9
20	.48	7.2	2.1	31.3	1.8	26.9	2.3	34.3
22	.01	2.9	.09	26.5	.10	29.4	.14	41.2
26	.09	3.0	.78	26.0	.58	19.5	1.58	52.7
27	.06	11.3	.10	18.9	.17	32.1	.20	37.8
30	0	0	.06	30.0	.06	30.0	.08	40.0
31	0	0	.05	33.3	.05	33.3	.06	33.3
33	.02	3.8	.09	17.0	.24	45.3	.18	34.0
34	.13	2.1	1.48	24.3	2.58	42.3	1.88	30.8
35	.05	3.5	.25	17.2	.54	37.2	.61	42.1
36	.02	6.9	.06	20.7	.13	44.9	.08	27.6
38	.20	6.3	1.36	42.5	.93	24.1	.66	20.7
40	.13	18.3	.19	26.8	.27	38.0	.12	16.9

TABLE 5(a): MORPHOLOGY: BASIC DATA

Morphology: Surface Change

(Normal=0; Mild=1; Moderate=2; Severe=3)

Case No.	Biopsy No.										
	1	2	3	4	5	6	7	8	9	10	11
1	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	1	0	0	0	1	0	0	0	0	0	0
4	2	3	3	3	0	3	3	3	0	0	0
5	0	0	1	0	0	0	1	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	2	0	2	2	3	1	1	1	0	0	0
8	3	0	1	1	0	1	-1	0	2	0	0
9	0	-1	0	0	0	0	0	0	0	0	0
10	0	0	0	-1	-1	0	3	0	0	0	0
11	0	0	1	1	0	0	0	-1	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0
13	2	2	2	3	1	0	2	2	1	0	0
14	2	2	1	1	1	1	1	1	1	1	1
15	0	0	0	0	0	0	0	1	1	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	2	0	1	1	1	1	-1
19	0	0	0	0	0	0	0	0	0	0	0
20	0	-2	0	0	3	0	0	0	1	0	1
21	0	0	0	0	0	0	0	2	0	0	-1
22	0	0	0	0	1	0	0	0	2	2	2
23	0	-0	0	0	0	0	0	0	0	0	0
24	0	0	-1	0	0	0	0	0	0	0	0
25	0	1	1	1	-1	2	1	1	0	2	-1
26	1	1	-1	2	2	1	2	0	0	0	0
27	1	1	1	3	0	1	1	1	-1	0	0
28	0	-1	1	1	1	0	1	2	0	0	1
29	0	0	0	0	0	0	0	0	0	0	-1
30	-1	0	0	0	0	0	0	0	2	1	1
31	0	1	1	3	2	2	2	3	0	0	0
32	1	1	3	3	-1	3	-1	3	3	2	2
33	0	0	0	0	0	0	0	-1	0	0	0
34	3	3	0	0	3	3	0	0	3	3	3
35	0	1	0	1	0	0	0	1	-1	0	0
36	0	2	3	3	1	0	1	2	1	0	0
37	0	0	0	0	0	0	0	0	0	0	0
38	1	1	0	0	1	1	0	0	2	-1	1
39	0	0	0	0	0	0	0	0	0	0	0
40	-1	0	0	0	0	0	0	0	0	0	0

TABLE 5(b)

Morphology: Round Cell Infiltrate

(Normal=0; Mild=1; Moderate=2; Severe=3)

Case No.	Biopsy No.										
	1	2	3	4	5	6	7	8	9	10	11
1	0	2	3	2	0	2	2	3	0	1	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	2	3	3	3	3	3	3	1	0	0	2
5	0	0	1	1	0	2	2	1	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	3	3	3	3	3	3	3	3	3	0	0
8	3	3	3	2	2	3	-1	3	3	2	3
9	0	-1	1	1	1	1	0	2	0	0	0
10	0	0	0	-1	-1	0	0	0	0	0	0
11	2	3	2	2	0	-1	2	3	0	0	0
12	2	1	1	1	0	0	2	2	0	0	0
13	3	3	3	2	1	1	3	3	2	1	2
14	3	3	3	3	3	3	3	3	3	1	2
15	1	3	3	2	1	3	3	3	1	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	2	0	0	0	3	2	3
18	3	2	2	2	3	1	3	3	3	3	-1
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	1	0	0	0	0	0	0
21	0	0	0	0	0	0	0	1	0	0	-1
22	2	1	1	1	2	1	1	1	3	3	3
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	-1	0	0	0	0	0	1	0	0
25	3	2	2	2	-1	2	3	3	1	2	-1
26	1	1	-1	1	0	-1	-1	1	2	3	3
27	3	3	3	3	1	2	2	2	-1	1	1
28	2	2	2	2	1	1	3	2	2	1	3
29	0	0	0	0	0	0	0	0	0	0	-1
30	-1	3	2	2	2	2	2	2	3	2	3
31	0	3	3	3	3	3	3	3	0	0	0
32	3	3	3	3	-1	3	-1	3	3	3	2
33	1	1	1	2	2	2	2	3	1	1	1
34	3	3	0	0	3	3	0	0	3	2	3
35	1	1	1	2	2	1	2	1	0	0	0
36	2	3	3	3	2	1	3	3	1	1	1
37	0	0	0	0	0	0	0	0	0	0	0
38	3	3	2	3	-1	3	3	3	3	3	3
39	0	1	0	0	0	0	0	1	0	0	0
40	-1	1	2	2	1	2	1	1	0	0	0

TABLE 5(c)

Morphology: Depth of Infiltrate

(Superficial=0; Full Thickness=1)

Case No.	Biopsy No:										
	1	2	3	4	5	6	7	8	9	10	11
1	0	0	1	0	0	0	0	1	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	1	0	1	1	1	1	0	0	0	1
5	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	0	1	0	0	1	1	0	1	0	0	0
8	1	0	0	1	0	1	-1	1	1	0	0
9	0	-1	0	0	0	1	0	0	0	0	0
10	0	0	0	-1	-1	0	0	0	0	0	0
11	0	0	0	1	0	0	1	1	0	0	0
12	1	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0
14	1	1	1	1	0	0	0	0	0	0	1
15	0	1	1	0	0	1	0	1	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	1	0	0	0	1	1	1
18	1	1	1	0	0	0	1	1	0	1	-1
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	-1
22	0	0	0	0	0	0	0	0	1	1	1
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	-1	0	0	0	0	0	0	0	0
25	1	1	1	1	-1	0	0	0	0	0	-1
26	0	0	-1	0	0	-1	-1	0	1	1	1
27	1	0	0	0	0	0	0	0	-1	0	0
28	0	1	1	1	0	0	1	1	0	0	0
29	0	0	0	0	0	0	0	0	0	0	-1
30	-1	1	1	0	0	0	0	1	0	0	1
31	0	0	1	1	1	1	1	1	0	0	0
32	0	0	0	1	-1	0	-1	1	0	0	0
33	0	0	0	1	0	0	0	0	0	0	0
34	1	1	0	0	0	1	0	0	0	0	1
35	0	0	0	0	0	0	0	0	0	0	0
36	1	1	1	1	0	0	1	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0
38	1	1	0	1	-1	1	1	-1	0	0	1
39	0	0	0	0	0	0	0	0	0	0	0
40	-1	0	0	0	0	0	0	0	0	0	0

TABLE 5(d)

Morphology: Polymorphs

(Normal=0; Mild=1; Moderate=2; Severe=3)

Case No. Biopsy No.

	1	2	3	4	5	6	7	8	9	10	11
1	0	1	0	0	0	0	1	1	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	2	0	2	1	1	1	1	1	0	0	1
5	0	0	1	0	0	0	1	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	1	1	2	1	3	1	0	1	2	0	0
8	3	2	2	2	2	2	-1	1	3	0	0
9	0	-1	0	0	0	0	0	0	0	0	0
10	0	0	0	-1	-1	0	0	0	0	0	0
11	0	0	0	1	0	0	1	0	0	0	0
12	0	0	1	1	0	0	1	0	0	0	0
13	2	1	2	1	1	0	1	3	2	1	0
14	2	2	2	2	2	2	2	1	1	0	2
15	0	2	2	0	0	1	1	1	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0
18	0	1	0	0	1	0	1	1	1	1	1
19	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	-1
22	0	0	0	0	1	0	0	1	1	1	1
23	0	0	0	0	0	0	0	0	0	0	0
24	0	0	-1	0	0	0	0	0	0	0	0
25	1	1	1	1	1	-1	1	1	1	1	-1
26	1	1	0	1	1	2	1	1	2	1	2
27	0	2	1	3	0	2	1	1	-1	0	1
28	1	0	0	2	1	1	2	1	3	1	3
29	0	0	0	0	0	0	0	0	0	0	-1
30	-1	0	0	0	1	1	1	0	1	0	0
31	0	0	1	1	1	1	1	1	0	0	0
32	1	1	2	2	-1	3	-1	2	3	3	2
33	1	0	0	0	0	0	2	1	0	0	0
34	2	2	0	0	3	3	0	0	3	2	3
35	1	0	0	1	0	0	1	0	0	0	0
36	1	1	2	3	1	0	1	2	1	0	1
37	0	0	0	0	0	0	0	0	0	0	0
38	1	2	1	2	2	3	2	2	2	2	2
39	0	0	0	0	0	0	0	0	0	0	0
40	-1	1	1	1	0	2	1	1	1	0	0

TABLE 5(e)

Morphology: Neck Changes

(Normal=0; Mild=1; Moderate=2; Severe=3)

Case No. Biopsy No.

	1	2	3	4	5	6	7	8	9	10	11
1	1	2	3	2	1	2	2	3	0	0	1
2	0	0	0	0	0	0	0	0	0	0	0
3	3	3	2	1	2	3	2	1	0	0	1
4	3	3	3	3	3	3	3	3	1	1	2
5	0	0	3	2	0	3	3	1	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0
7	3	3	2	3	3	3	3	3	3	1	1
8	3	3	3	3	2	3	-1	3	3	1	1
9	0	-1	1	1	0	2	1	1	0	0	0
10	0	0	0	-1	-1	0	3	2	0	0	0
11	1	2	2	3	1	1	2	2	0	0	0
12	2	0	2	2	0	0	2	2	0	0	1
13	3	3	3	3	2	1	3	3	2	1	0
14	3	3	3	3	3	3	3	3	3	2	3
15	0	3	3	1	0	3	3	1	0	0	0
16	0	0	0	0	0	0	0	1	0	0	0
17	1	0	2	3	3	2	3	3	-1	-1	-1
18	3	3	2	0	3	1	3	3	2	2	-1
19	0	0	0	2	1	0	0	0	1	0	0
20	2	2	2	2	3	1	0	1	3	0	3
21	0	0	0	1	0	1	1	2	0	0	-1
22	3	3	3	3	3	2	2	3	3	3	3
23	0	0	0	3	0	0	2	0	0	0	0
24	0	3	-1	0	0	0	1	2	0	0	0
25	3	3	3	3	-1	3	3	3	0	2	-1
26	3	3	3	3	3	3	3	3	3	-1	3
27	2	3	2	3	1	3	2	3	-1	0	1
28	3	3	3	3	2	1	3	3	2	1	2
29	0	0	3	3	0	2	0	2	0	0	-1
30	-1	2	1	1	2	1	2	2	1	1	2
31	1	3	3	3	3	3	3	3	0	0	0
32	2	3	3	3	-1	3	-1	3	3	3	3
33	1	0	0	2	2	1	1	3	1	1	2
34	3	3	-1	0	3	3	1	3	3	3	3
35	1	2	2	2	1	2	2	3	0	0	0
36	2	3	3	3	1	0	0	2	1	0	0
37	0	0	0	0	0	0	0	0	0	0	0
38	3	3	3	3	3	3	3	3	3	3	3
39	0	2	0	0	0	0	0	1	0	0	0
40	-1	2	0	2	1	3	1	1	0	0	0

TABLE 6: TOTAL GASTRITIS SCORE PER BIOPSY

("F" = Fundic from Endoscopic Antrum)

Case No.	Biopsy No.										
	1	2	3	4	5	6	7	8	9	10	11
1	F	5	7	4	F	4	5	8	0	1	1
2	F	F	0	0	F	F	0	0	0	0	0
3	4	3	2	1	4	0	0	0	0	0	1
4	9	10	11	11	8	11	11	8	1	1	6
5	F	F	6	3	F	5	7	2	0	0	0
6	F	0	0	0	F	F	0	0	0	0	0
7	9	8	9	9	13	9	7	9	8	1	1
8	13	8	9	9	F	10	-1	8	12	3	4
9	F	-1	2	2	F	4	1	3	0	0	0
10	0	0	0	-1	-1	F	6	2	0	0	0
11	3	5	5	8	1	2	6	7	0	0	0
12	5	1	4	4	F	F	5	4	0	0	1
13	10	9	10	9	F	F	9	11	7	3	2
14	11	11	10	10	9	9	9	8	8	4	9
15	F	9	9	3	1	8	7	7	2	0	0
16	0	0	0	0	F	F	0	1	0	0	0
17	1	0	2	3	6	2	3	3	4	3	4
18	7	8	5	2	F	2	9	9	7	8	-1
19	0	0	0	2	F	0	0	0	1	0	0
20	F	F	2	2	7	1	0	1	4	0	4
21	0	F	0	1	F	1	1	5	0	0	-1
22	5	4	4	4	7	3	3	5	10	10	10
23	0	0	0	3	F	0	2	0	0	0	0
24	0	3	-1	0	F	0	1	2	1	0	0
25	8	8	8	8	-1	8	8	8	2	7	-1
26	6	6	-1	7	6	6	6	5	8	8	9
27	7	9	7	12	2	8	6	8	-1	1	3
28	6	7	7	9	F	F	10	9	7	3	9
29	0	0	3	3	0	2	0	2	0	0	-1
30	-1	6	4	3	F	4	5	5	7	4	7
31	F	7	9	11	10	10	10	11	0	0	0
32	7	8	11	12	-1	12	-1	12	12	11	9
33	3	F	1	5	4	3	5	7	2	2	3
34	12	12	0	0	12	13	1	3	12	10	13
35	3	4	3	6	F	3	5	5	0	0	0
36	6	10	12	13	F	F	6	9	4	1	2
37	0	0	0	0	F	F	0	0	0	0	0
38	9	10	6	9	10	11	9	9	10	9	10
39	0	3	0	0	0	0	0	2	0	0	0
40	-1	4	3	5	F	7	3	3	1	0	0

TABLE 7(a): WHOLE GASTRIC INDIVIDUAL MEAN GASTRITIS SCORES

Case No.	Surface Change	Activity Index	Depth of Infiltrate	Polymorphs	Neck Changes
1	0	1.36	.18	.27	1.54
2	0	0	0	0	0
3	.33	0	0	0	2.17
4	1.82	2.09	.54	.91	2.54
5	.18	.64	0	.18	1.09
6	0	0	0	0	0
7	1.09	2.45	.36	1.09	2.54
8	.80	2.70	.50	1.70	2.20
9	0	.60	.10	0	.60
10	.33	0	0	0	.56
11	.20	1.36	.27	.18	1.27
12	0	.82	.09	.27	1.00
13	1.18	2.18	0	1.27	2.18
14	1.18	2.73	.45	1.64	2.91
15	.18	1.82	.36	.64	1.23
16	0	0	0	0	.09
17	0	.91	.36	0	2.13
18	.60	2.60	.60	.60	2.20
19	0	0	0	0	.44
20	.64	.09	0	0	1.78
21	.20	.10	0	0	.50
22	.64	1.73	.27	.45	2.82
23	0	0	0	0	.45
24	0	.10	0	0	.60
25	1.00	2.22	.44	1.0	2.56
26	.90	1.50	.38	1.18	3.00
27	.90	2.10	.10	1.10	2.00
28	.70	1.91	.45	1.09	2.36
29	0	0	0	0	1.00
30	.40	2.30	.40	.40	1.50
31	1.27	1.91	.60	.54	2.00
32	2.00	2.89	.22	2.11	2.89
33	0	1.54	.09	.36	1.27
34	1.91	1.82	.36	1.64	2.50
35	.30	1.0	0	.27	1.36
36	1.18	2.09	.45	1.18	1.36
37	0	0	0	0	0
38	.70	2.9	.70	1.91	3.00
39	0	.18	0	0	.27
40	0	1.0	0	.80	1.00

TABLE 7(b): WHOLE ANTRAL INDIVIDUAL MEAN GASTRITIS SCORES

Case No.	Surface Change	Activity Index	Depth of Infiltrate	Polymorphs	Neck Changes
1	0	2.33	.33	.50	2.33
2	0	0	0	0	0
3	.40	0	0	0	2.40
4	2.50	2.63	.63	1.12	3.00
5	.40	1.40	0	.40	2.40
6	0	0	0	0	0
7	1.50	3.00	.50	1.25	2.88
8	1.00	2.83	.67	2.0	3.00
9	0	1.00	.20	0	1.20
10	.60	0	0	0	1.00
11	.29	1.88	.38	.25	1.75
12	0	1.50	.17	.50	1.67
13	2.17	2.83	0	1.67	3.00
14	1.25	3.00	.50	1.88	3.00
15	1.43	2.57	.57	1.00	2.00
16	0	0	0	0	.17
17	0	.25	.13	0	2.13
18	.29	2.42	.71	.43	2.14
19	0	0	0	0	.40
20	.50	.17	0	0	1.50
21	.33	.17	0	0	.83
22	.13	1.25	0	.25	2.75
23	0	[illegible]	0	0	.71
24	0	[illegible]	0	[illegible]	1.00
25	1.00	2.42	.57	[illegible]	3.00
26	1.29	.80	0	1.00	3.00
27	1.13	2.38	.13	1.25	2.38
28	1.00	2.17	.83	1.00	3.00
29	0	0	0	0	1.25
30	0	2.17	.50	.33	1.50
31	2.00	3.00	.86	.86	3.00
32	2.33	3.00	.33	1.83	2.83
33	0	2.17	.17	.66	1.66
34	1.5	1.5	.38	1.25	2.29
35	.43	1.29	0	.43	2.00
36	1.83	2.83	.83	1.67	2.17
37	0	0	0	0	0
38	.50	2.86	.86	1.86	3.00
39	0	.25	0	0	.38
40	0	1.5	0	1.17	1.43

TABLE 7(c): DISTAL ANTRAL INDIVIDUAL MEAN GASTRITIS SCORES

Case No.	Surface Change	Activity Index	Depth of Infiltrate	Polymorphs	Neck Changes
1	0	2.50	.50	.50	2.50
2	0	0	0	0	0
3	0	0	0	0	2.00
4	3.00	2.50	.50	1.25	3.00
5	.50	1.25	0	.50	2.25
6	0	0	0	0	0
7	1.50	3.00	.25	1.00	2.75
8	.67	2.67	.67	1.67	3.00
9	0	1.00	0	0	1.00
10	1.00	0	0	0	1.67
11	.67	2.25	.75	.50	2.25
12	0	1.50	0	.75	2.00
13	2.25	2.75	0	1.75	3.00
14	1.00	3.00	.50	1.75	3.00
15	.25	2.75	.50	1.00	2.00
16	0	0	0	0	.25
17	0	0	0	0	2.75
18	.50	2.5	.75	.50	2.0
19	0	0	0	0	1.00
20	0	0	0	0	1.25
21	.50	.25	0	0	1.00
22	0	1.00	0	.25	2.75
23	0	0	0	0	1.25
24	0	0	0	0	1.00
25	1.00	2.50	.50	1.00	3.00
26	1.33	1.00	0	.75	3.00
27	1.50	2.50	0	1.50	2.50
28	1.25	2.25	1.00	1.25	3.00
29	0	0	0	0	2.00
30	0	2.00	.50	.25	1.5
31	2.25	3.00	1.00	1.00	3.00
32	3.00	3.00	.67	2.00	3.00
33	0	2.00	.25	.75	1.50
34	0	0	0	0	1.33
35	.50	1.50	0	.50	2.25
36	2.25	3.0	.75	2.0	2.0
37	0	0	0	0	0
38	0	2.75	.75	1.75	3.00
39	0	.25	0	0	.25
40	0	1.5	0	1.0	.75

TABLE 7(d): WHOLE FUNDIC INDIVIDUAL MEAN GASTRITIS SCORES

Case No.	Surface Change	Activity Index	Depth of Infiltrate	Polymorphs	Neck Changes
1	0	.33	0	0	.33
2	0	0	0	0	0
3	0	0	0	0	.33
4	0	.67	.33	.33	1.33
5	0	0	0	0	0
6	0	0	0	0	0
7	0	1.00	0	.67	1.67
8	.67	2.67	.33	1.00	1.67
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	.33
13	.33	1.67	0	1.00	1.00
14	1.00	2.00	.33	1.00	2.67
15	.33	.33	0	0	0
16	0	0	0	0	0
17	0	2.67	1.00	0	-1
18	1.00	3	.50	1.00	2.00
19	0	0	0	0	.33
20	.67	0	0	0	2.00
21	0	0	0	0	0
22	2.00	3.00	1.00	1.00	3.00
23	0	0	0	0	0
24	0	.33	0	0	0
25	.67	1.00	0	1.00	1.00
26	0	2.67	1.00	1.67	3.00
27	0	1.00	0	.50	.50
28	.33	2.00	0	2.30	1.67
29	0	0	0	0	0
30	1.33	2.67	.33	.33	1.33
31	0	0	0	0	0
32	2.33	2.67	0	2.67	3.00
33	0	1.00	0	0	1.33
34	3.00	2.67	.33	2.67	3.00
35	0	0	0	0	0
36	.33	1.00	0	.67	.33
37	0	0	0	0	0
38	1.00	3.00	.33	2.00	3.00
39	0	0	0	0	0
40	0	0	0	.33	0

TABLE 8: TOTAL MEAN GASTRITIS SCORES

Case No.	Whole Gastric	Whole Antral	Distal Antral	Whole Fundal
1	3.35	5.49	6.00	.67
2	0	0	0	0
3	2.50	2.80	2.00	1.00
4	7.81	4.89	10.25	2.67
5	2.09	4.60	4.50	0
6	[illegible]	0	0	0
7	7.33	4.13	8.50	3.33
8	7.00	4.50	8.68	6.33
9	1.30	2.40	2.00	0
10	.89	1.60	2.67	0
11	3.28	4.55	6.42	0
12	2.18	3.84	4.25	.33
13	6.81	9.67	9.75	4.00
14	8.91	9.63	9.25	7.00
15	4.27	7.57	6.5	.67
16	.09	.17	.25	0
17	3.40	2.51	2.75	3.67
18	6.50	5.99	6.25	7.50
19	.44	.40	1.00	.33
20	2.46	2.17	1.25	2.67
21	.80	1.33	1.75	0
22	5.82	4.38	4.00	10.00
23	.45	.71	1.25	0
24	.70	1.00	1.00	.33
25	7.22	7.99	8.00	4.50
26	6.96	6.09	6.08	8.33
27	6.20	7.27	8.00	2.00
28	6.51	8.00	8.75	6.33
29	1.00	1.25	2.00	0
30	5.00	4.50	4.25	6.00
31	6.32	9.72	10.25	0
32	10.11	10.32	11.67	10.67
33	3.26	4.66	4.50	2.33
34	8.23	6.92	1.33	11.67
35	2.93	4.15	4.75	0
36	6.26	9.33	10.00	2.33
37	0	0	0	0
38	9.21	4.08	8.25	9.67
39	.45	.63	.50	0
40	2.8	4.10	3.25	.33

TABLE 9: GASTRITIS AND AGE

Anatomic Area	Total Mean Gastric Score	No. of Cases	Average Age (years)	Significance (unpaired t-test)	Significance Gastric Score ≤4 vs >4
Whole Gastric	≤1.00	11	38.4	p < .05	p < .0[illegible]
	1.01-4.00	11	41.8	p < .01	
	4.01-7.00	10	55.1	N.S.	
	>7.00	8	51.4		
Whole Antral	≤1.00	8	4.28	N.S.	p < .001
	1.01-4.00	8	33.1	p < .01	
	4.01-7.00	11	53.9	N.S.	
	7.01-9.00	4	46.5	p < .05	
	>9.00	9	50.9		
Distal Antral	≤1.00	7	44.1	N.S.	p < .001
	1.01-4.00	11	44.0	N.S.	
	4.01-7.00	9	41.4	p < .05	
	7.01-9.00	7	47.7	p < .05	
	>9.00	6	51.8		
Whole Fundal	0	14	39.1	N.S.	p < .001
	0 ≤1.00	7	45.0	N.S.	
	1.01-4.00	8	48.0	N.S.	
	4.01-7.00	5	54.0	N.S.	
	>7.00	6	54.5		

TABLE 10: AGE AND GASTRITIS

Total Mean Gastritis Score Per Anatomic Area	Age Groups (years) 20-29 (5 cases)	30-39 (10 cases)	40-49 (12 cases)	50-59 (6 cases)	60-89 (7 cases)
Whole Gastric	2.02	3.09	4.66	6.21	6.41
		($p < .05$)	($p < .01$)	($p < .01$)	(N.S.)
Whole Fundal	.71	2.19	1.94	4.11	5.90
		($p < .01$)	(N.S.)	($p < .01$)	($p < .05$)
Whole Antral	2.51	3.43	5.68	7.0	6.61
Distal Antral	2.90	3.83	5.40	6.34	5.56
Whole Gastric Individual Mean Gastritis Score					
Surface Change	.11	.40	.44	.66	.98
Activity Index (Round Cell Infiltrate)	.49	.90	1.12	1.72	1.79
Depth of Infiltrate	.04	.15	.19	.33	.34
Polymorphs	.13	.35	.54	.94	.94
Neck Changes	.67	1.39	1.46	1.92	2.10

TABLE 11(a): BILE REFLUX AND GASTRITIS

Gastritis Scores: Total Mean Score per Anatomic Area:	Bile Refluxers (TBA ≥ .40 mM/L) (18 cases)	Non Refluxers (TBA < .40 mM/L) (22 cases)
Whole Gastric	6.25 ± 1.12 (S.D.)	3.07 ± 1.06 (S.D.) ($p < .001$)
Whole Antral	6.66	3.67
Distal Antral	6.28	3.99
Whole Fundal	5.14	1.47
Lesser Curve Antral	6.94	3.72
Proximal Antral	7.05	3.35
Whole Gastric:		
Individual Mean Gastritis Scores:		
Surface Change	.83	.29
Activity Index (Round Cell Infiltrate)	1.77	.79
Depth of Infiltrate	.30	.12
Polymorphs	.91	.31
Neck Changes	1.97	1.15

TABLE 11(b): BILE REFLUX AND VARIOUS OTHER FACTORS

Factors	Bile Refluxers	Non-Refluxers
No. of Cases	18	22
Average Age (years)	53.0	40.4
pH	4.34 ± 2.43	3.22 ± 1.53
Sex	13 F/5 M	12 F/10 M
Gallbladder Disease (%)	44	27
Personal Habits:		
Smokers (%)	50	40.9
Coffee Drinkers (%)	72.2	81.8
Alcohol Drinkers (%)	22.2	50
Intestinal Metaplasia (%)		
Absent	27.8	77.3
Mild, Moderate	38.8	13.6
Severe	33.3	9
Anorexia/Weightloss (%)	55.5	22.7
Relief with Antacids (%)	50	68

TABLE 12: AMOUNT OF BILE REFLUXED VS. GASTRITIS

Total Mean Gastritis Score per Anatomic Area	Amount of Bile Refluxed (μM) 0-4 (12 cases)		4-15 (11 cases)		15-75 (7 cases)		>75 (5 cases)
Whole Gastric	33.3	($p < .01$)	4.74	($p < .01$)	5.89	(N.S.)	6.04
Whole Antral	4.17		5.19		6.78		5.93
Whole Fundal	1.09	($p < .01$)	3.51	(N.S.)	3.52	($p < .01$)	6.33
Lesser Curve Antral	3.87		5.39		6.98		5.76
Whole Gastric Individual Mean Gastritis Scores:							
Surface Change	.34		.48		.83		.89
Activity Index (Round Cell Infiltrate)	.81		1.36		1.76		2.16
Depth of Infiltrate	.09		.26		.26		.29
Polymorphs	.32		.49		1.01		1.00
Neck Changes	1.25		1.64		1.61		2.32

TABLE 13: TOTAL BILE ACID CONCENTRATION VS. GASTRITIS

	Total Bile Acids Concentration (mM/L)							
	0-.10		.11-.39		.40-1.0		>1.0	
No. of Cases	8		8		9		9	
Total Mean Gastritis Score								
Whole Gastric	2.78	(N.S.)	3.36	($p < .01$)	6.26	(N.S.)	6.23	
Whole Antral	3.50		3.83		6.97		5.89	
Whole Fundal	.84		2.10		4.38		5.89	
Distal Antral	3.51		4.46		7.36		5.19	
Proximal Antral	3.50		3.20		6.57		7.52	
Lesser Curve Antral	3.22		4.22		7.38		6.50	
Individual Mean (Whole Gastric) Gastritis Scores								
Surface Change	.33		.24		.86		.79	
Activity Index	.67		.88		2.01		1.52	
Polymorphs	.28		.33		.93		.89	
Depth	.10		.14		.31		.29	
Mech Changes	.99		1.30		1.97		1.96	

TABLE 14: GASTRITIS AND BILE REFLUX

	Total Mean Gastritis Score per Anatomic Area	Mean Concentration Total Bile Acids ± S.D. (mM/L)	Average Amount Total Bile Acid ± S.D. (μM)	% of Cases Refluxers
	≤ 1.00	.22 ± .31	8.33 ± 13.4	9
Whole	1.01 - 4.00	2.04 ± 3.09	43.4 ± 77.3	45
Gastric	4.01 - 7.00	.96 ± 1.42	18.2 ± 23.8	60
	> 7.00	2.04 ± 2.67	118.5 ±233	75
	0	.79 ± 1.69	16.2 ± 26.4	28.6
Whole	0 - 1.00	.29 ± .33	5.03 ± 7.52	14.3
Fundal	1.01 - 4.00	1.6 ± 2.83	48.38 ± 81.6	62.5
	4.01 - 7.00	.56 ± .56	8.4 ± 6.4	60
	> 7.01	3.61 ± 2.41	190.8 ±271.9	83.3
	≤ 1	.23 ± .35	9.31 ± 15.0	25
Whole	1.01 - 4.00	1.92 ± 3.54	47.15 ± 95.7	12.5
Antral	4.01 - 7.00	2.32 ± 2.82	98.3 ±212.4	22.7
	7.01 - 9.00	.27 ± .21	6.67 ± 5.3	25
	> 9.00	1.01 ± 1.20	27.97 ± 34.3	77.8
	≤ 1	.26 ± .37	10.6 ± 15.8	14.3
Distal	1.01 - 4.00	2.16 ± 3.48	104.3 ±221.6	36.4
Antral	4.01 - 7.00	2.16 ± 2.44	31.7 ± 36.6	44.4
	7.01 - 9.00	.96 ± 1.38	22.8 ± 39.48	42.9
	> 9.00	.55 ± .39	18.95 ± 13.84	83.3

TABLE 15: INDIVIDUAL MEAN GASTRITIS SCORES VS. REFLUX

	Whole Gastric Individual Mean Gastritis Scores	No. of Cases	Average Age (years)	Concentration TBA (mM/L)	% of Cases Refluxers	Amount TBA (μM)
Polymorphs	0	15	39.07	.935 ± 2.45	13	26.8 ± 68.6
	.01 - 1.00	13	47.23	1.23 ± 1.74	62	23.3 ± 27.4
	> 1.00	12	53.61	1.74 ± 2.49	67	85.1 ±196.9
Surface Change	0	15	42.93	.33 ± .39	20	10.6 ± 12.9
	.01 - 1.00	16	44.94	2.36 ± 2.84	56	47.9 ± 72.5
	≥ 1.00	9	53.44	1.30 ± 2.49	67	93.9 ±224.8
Activity Index (Round Cell Infiltrate)	0	9	40 ± 12.5	.25 ± .34	11	9.15
	.01 - 1.00	10	41.4 ± 15.4	2.09 ± 3.29	33	48.85
	1.01 - 2.00	9	51.0 ± 17.0	2.02 ± 2.74	67	109.78
	> 2.00	12	50.9 ± 12.7	.875 ± 1.12	67	23.67

TABLE 16: RADIONUCLIDE REFLUX AND GASTRITIS

	Refluxers (4 cases)		Non-Refluxers (12 cases)
Average Age (years)	46.25		45.17
Sex Distribution	2 M/2 F		3 M/9 F
Total Symptom Score	12.5 ± 5.12		13.1 ± 3.71
Personal Habits:			
Smoking	50%		42%
Alcohol	50%		50%
Coffee	100%		83%
Concentration of Total Bile Acids (mM/L)	2.4 ± 3.9		1.68 ± 2.81
Total Mean Gastritis Score:			
Whole Gastric	4.57 ± 2.76	(N.S.)	4.09 ± 2.82
Whole Antral	4.36 ± 1.88	(N.S.)	5.01 ± 3.40
Whole Fundal	5.72 ± 5.45	(N.S.)	2.76 ± 2.93
Distal Antral	3.6 ± 1.88	(N.S.)	5.07 ± 3.35

TABLE 17: LYSOLECITHIN AND GASTRITIS

	Amount of Lysolecithin		
	0	Trace, 1+, 2+	> 2+
No. of Cases	6	5	4
Average Age (years)	47.5	48.6	58.3
Total Symptom Score	10.67	10.4	14.8
Total Mean Gastritis Score:			
Whole Gastric	5.6 ± 3.39 (N.S.)	5.54 ± 2.14 (N.S.)	6.71 ± 2.58
Whole Antral	6.45 ± 3.76 (N.S.)	6.52 ± 2.60 (N.S.)	6.07 ± 2.50
Whole Fundal	3.95 ± 4.19 (N.S.)	4.27 ± 3.51 ($p < .02$)	8.09 ± 3.34
Distal Antral	6.97 ± 3.97 (N.S.)	6.44 ± 2.53 (N.S.)	4.23 ± 3.04

TABLE 18: AGE AND BILE REFLUX

Age (years)	No. of Cases	Concentration of Total Bile Acids	Amount of Total Bile Acids	Percent Refluxing	pH
20-29	5	.45 ± .58	1.32 ± 15.0	20	3.52 ± 1.61
30-39	10	1.5 ± 3.3	37.9 ± 40.4	30	4.12 ± 1.67
40-49	12	.86 ± 1.8	17.8 ± 27.1	42	2.70 ± 1.84
50-59	6	.94 ± 1.80	27.4 ± 51.1	33	3.88 ± 2.38
≥60	7	2.4 ± 3.0	124.9 +265.3	100	4.92 ± 2.52

TABLE 19: BILE REFLUX AND AGE

Concentration of Total Bile Acids (mM/L)	No. of Cases	Average Age (years)	Significance
$0 \leq 0.10$	8	43.1	
$.11 \leq .39$	8	41.5	N.S.
$.40 \leq 1.0$	9	54.9	$p < .01$
> 1.0	9	51.2	N.S.

TABLE 20: AMOUNT OF BILE REFLUXED VS. AGE

Amount of Total Bile Acids (μM)	No. of Cases	Average Age (years)	Significance
0-4	12	43.0	
4-15	11	46.8	N.S.
15-75	7	52.3	$p < .05$
>75	5	54.8	N.S.

TABLE 21: ROLE OF GALLBLADDER DISEASE

Factors	Normal Gallbladder	Diseased (or removed) Gallbladder	Significance
No. of Cases	26	14	
Average Age (years)	44.7	48.6	N.S.
Total Symptom Score	11.0 ± 5.1	12.0 ± 5.6	N.S.
Concentration of Total Bile Acids (mM/L)	.60± 1.25	3.26± 3.47	$p < .01$
Amount of Total Bile Acids (μM)	14.6 ± 21.1	123.8 ±227.1	$p < .05$
Present Refluxing	38.5	57.1	$p < .05$
pH	2.87 ± 1.26	5.31 ± 3.19	$p < .01$
Total Mean Gastritis Score:			
Whole Gastric	3.46 ± 2.82	5.14 ± 3.19	$p < .05$
Whole Antral	4.43 ± 3.71	5.39 ± 3.11	$p < .05$
Distal Antral	4.63 ± 3.65	4.77 ± 3.33	N.S.
Whole Fundal	1.54 ± 2.10	5.9 ± 4.83	$p < .01$

TABLE 22: ROLE OF SEX

	Male	Female	Significance
No. of Cases	15	25	
Average Age (years)	48.3	44.9	N.S.
Total Symptom Score	9.8 ± 3.4	12.4 ± 5.3	$p < .01$
Concentration of Total Bile Acids (mM/L)	.34 ± .28	1.83 ± 2.72	$p < .01$
Amount of Total Bile Acids (μM)	7.85 ± 5.58	68.5 ± 155.3	N.S.
Percent Refluxing	33	54	N.S.
pH	3.01	4.52	N.S.
Total Mean Gastritis Score:			
Whole Gastric	3.48 ± 1.31	5.06 ± 2.14	$p < .01$
Whole Antral	4.22 ± 2.36	5.58 ± 2.69	$p < .01$
Distal Antral	3.53 ± 1.43	5.12 ± 3.11	$p < .01$
Whole Fundal	1.54 ± 2.00	3.68 ± 2.60	$p < .01$

TABLE 23: BILE REFLUX VS. GASTRITIS

(Matched For Age, Sex and Gallbladder Disease)

	Refluxers	Non-Refluxers	Significance
No. of Cases	13	13	
Total Symptom Score	11.38 ± 5.38	12.84 ± 3.31	N.S.
Total Mean Gastritis Score:			
Whole Gastric	5.71 ± 3.09	2.63 ± 2.72	$p < .01$
Whole Fundal	4.10 ± 4.09	1.70 ± 2.64	$p < .05$
Distal Antral	6.71 ± 3.59	3.44 ±31	$p < .02$
Lesser Curve Antral	6.60 ± 3.60	2.76 ± 2.81	$p < .01$
Greater Curve Antral	6.50 ± 3.50	3.42 ± 3.45	$p < .01$
Individual Mean Gastritis Score:			
Whole Gastric:			
Activity Index	1.77 ± .97	.85 ± .99	$p < .02$
Surface Change	.80 ± .61	.21 ± .34	$p < .01$
Depth	.29 ± .24	.17 ± .21	N.S.
Polymorphs	.86 ± .73	.28 ± .41	$p < .01$
Whole Fundal:			
Activity Index	1.23 ± 1.21	.72 ± 1.06	N.S.
Surface Change	.59 ± .77	.13 ± .28	$p < .05$
Polymorphs	.65 ± .83	.31 ± .65	N.S.
Distal Antral:			
Activity Index	2.01 ± 1.03	.98 ± 1.17	$p < .05$
Surface Change	.97 ± 1.08	.31 ± .49	$p < .10$
Polymorphs	.99 ± .68	.33 ± .45	$p < .01$
Lesser Curve Antral:			
Activity Index	1.96 ± 1.05	.84 ± 1.10	$p < .02$
Surface Change	.94 ± .82	.19 ± .42	$p < .02$
Polymorphs	.89 ± .78	.27 ± .42	$p < .02$

TABLE 24: BILE REFLUX AND SYMPTOMS

Total Bile Acids	No. of Cases	Total Symptom Score
Concentration (mM/L)		
0- .10	8	12.5 ± 3.77
.11- .39	8	11.25± 4.94
.40-1.0	9	10.6 ± 4.52
>1.0	9	12.7 ± 6.90
Amount (μM)		
0- 4	I2	11.0 ± 4.98
4-15	11	10.8 ± 2.66
15-75	7	14.0 ± 4.60
>75	5	11.8 ± 8.75

TABLE 25: GASTRITIS AND SYMPTOMS

Total Mean Gastritis Score	No. of Cases	Total Symptom Score
Whole Gastric		
0 -1.0	11	11.18
1.01-4.0	11	11.0
4.01-7.0	10	8
>7.0	8	14.25
Whole Antral		
0 -1.0	8	12.0
1.01-4.0	8	11.4
4.01-7.0	11	10.9
7.01-9.0	4	10.0
>9.0	9	12.7
Whole Fundal		
0	14	10.79
.01-1.0	7	9.57
1.01-4.0	8	12.75
4.01-7.0	5	10.4
>7.0	6	14.8
Distal Antral		
0 -1.0	7	12.43
1.01-4.0	11	11.73
4.01-7.0	9	10.33
7.01-9.0	7	12.57
>9.0	6	10.17

TABLE 26: SYMPTOMS AND GASTRITIS

	0-7	8-10	11-15	>15
No. of Cases	8	10	12	10
Average Ages (years)	52.6	47.9	40.5	45.8
Total Mean Gastritis Score:				
Whole Gastric	5.10	4.36	2.92	6.37
Whole Antral	5.83	5.13	2.89	6.79
Individual Mean Gastritis Score:				
Surface Change	.60	.56	.17	.83
Activity Index	1.35	1.23	.56	1.98
Polymorphs	.77	.39	.09	1.06
Depth	.16	.23	.11	.34
Neck Changes	1.76	1.62	.98	1.88

TABLE 27

Bile Salt Analysis Procedure: Assay

	Blank(ml)	Test(ml)	CDCA Standards ml		
Buffer	2.0	2.0	2.0	2.0	2.0
Hydrazine	1.0	1.0	1.0	1.0	1.0
NAD	0.5	0.5	0.5	0.5	0.5
Bile	0.003	0.003	-	-	-
Enzyme	-	0.025	0.025	0.025	0.025
Boiled Enzyme	0.025	-	-	-	-
Chenodeoxycholate Acid	-	-	0.01	0.03	0.05

Figure 1: The Motility Tube After Modifications

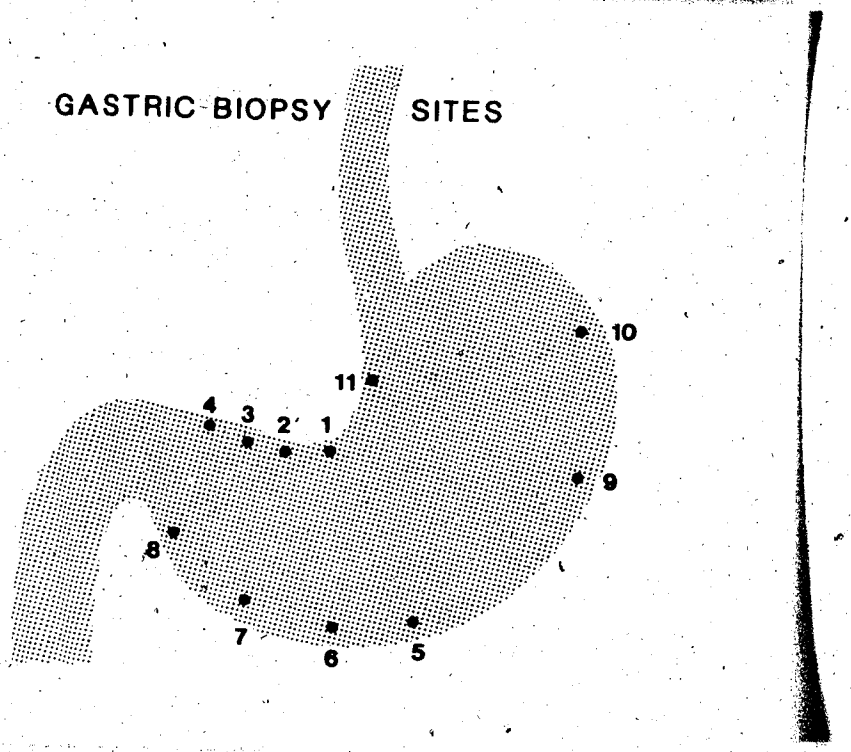


Figure 2: The Anatomic Sites of Gastric Biopsies

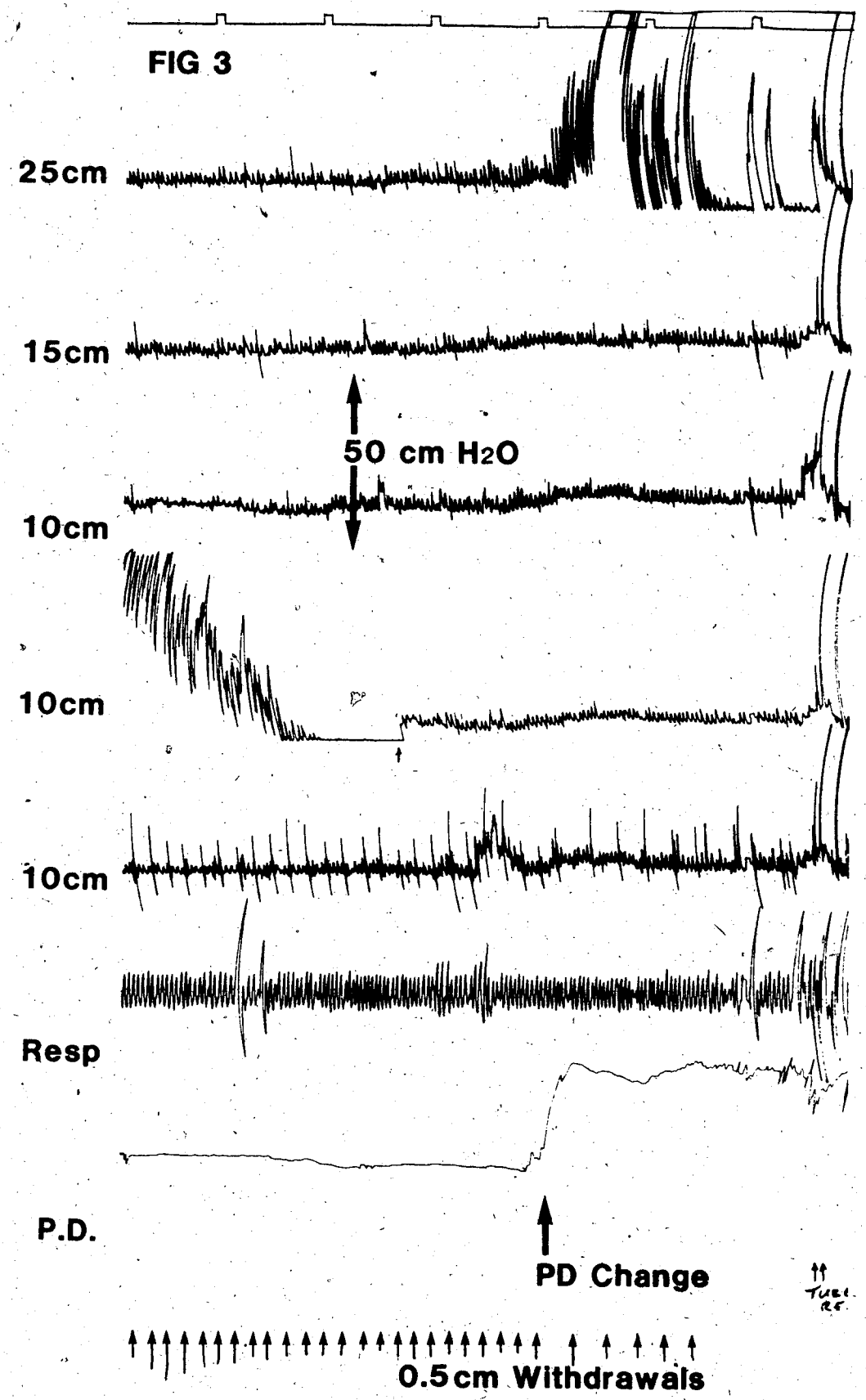


FIG 3
25cm
15cm
50 cm H2O
10cm
10cm
10cm
Resp
P.D.
PD Change
0.5cm Withdrawals

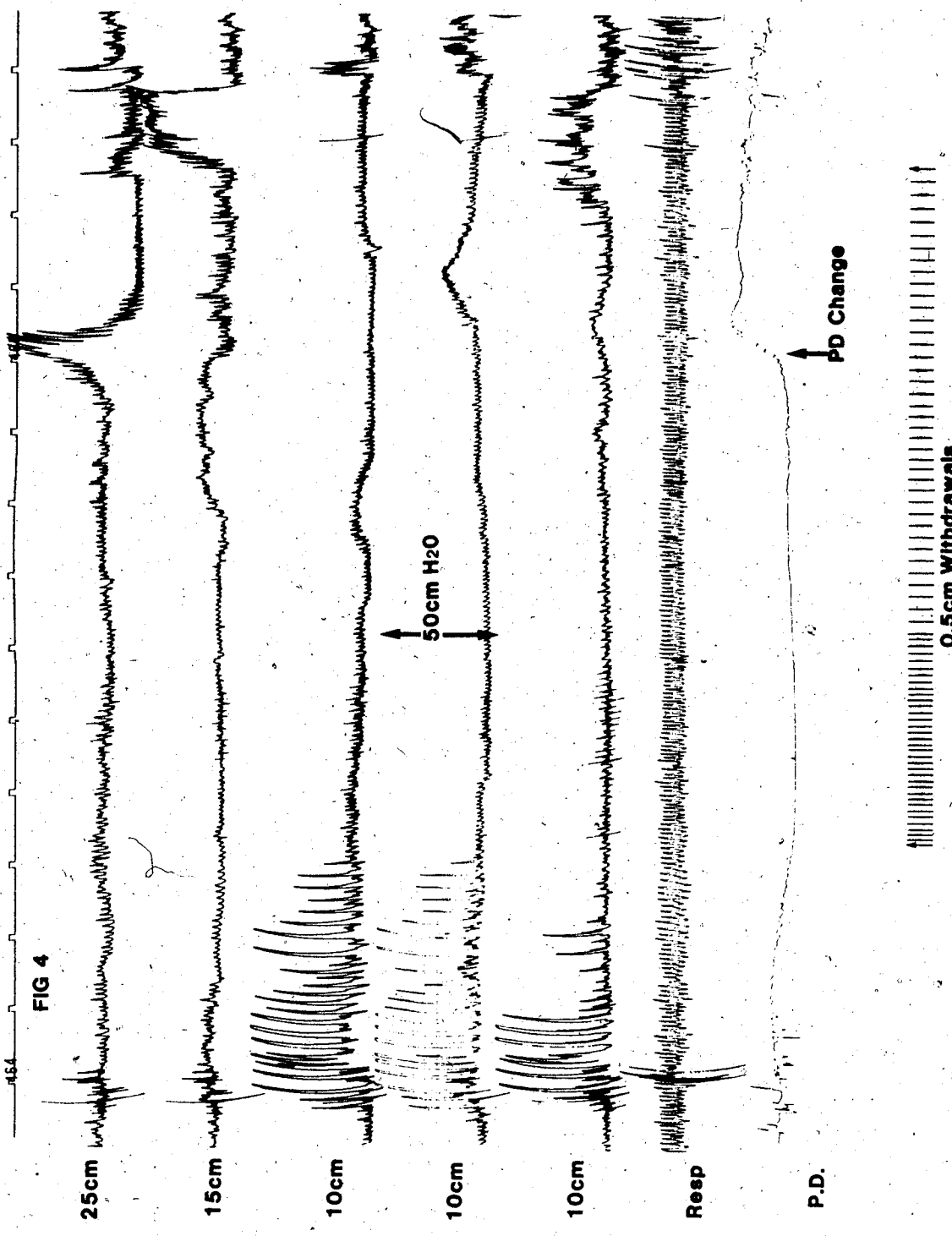
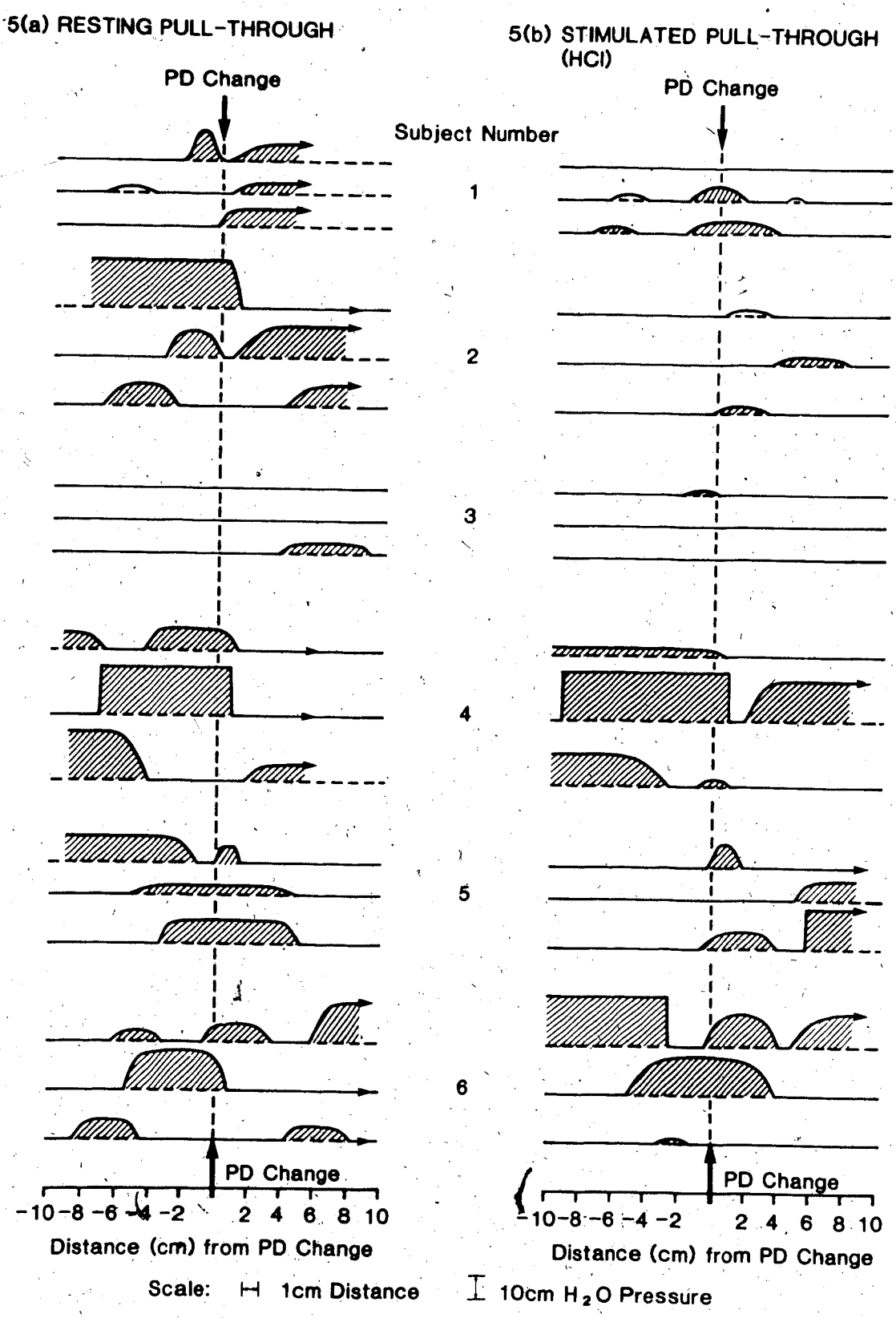


FIG 4
25cm
15cm
10cm
50cm H2O
10cm
10cm
Resp
P.D.
PD Change
0.5cm Withdrawals

Figure 5: PRESSURE ELEVATIONS AT THE GASTRODUODENAL JUNCTION



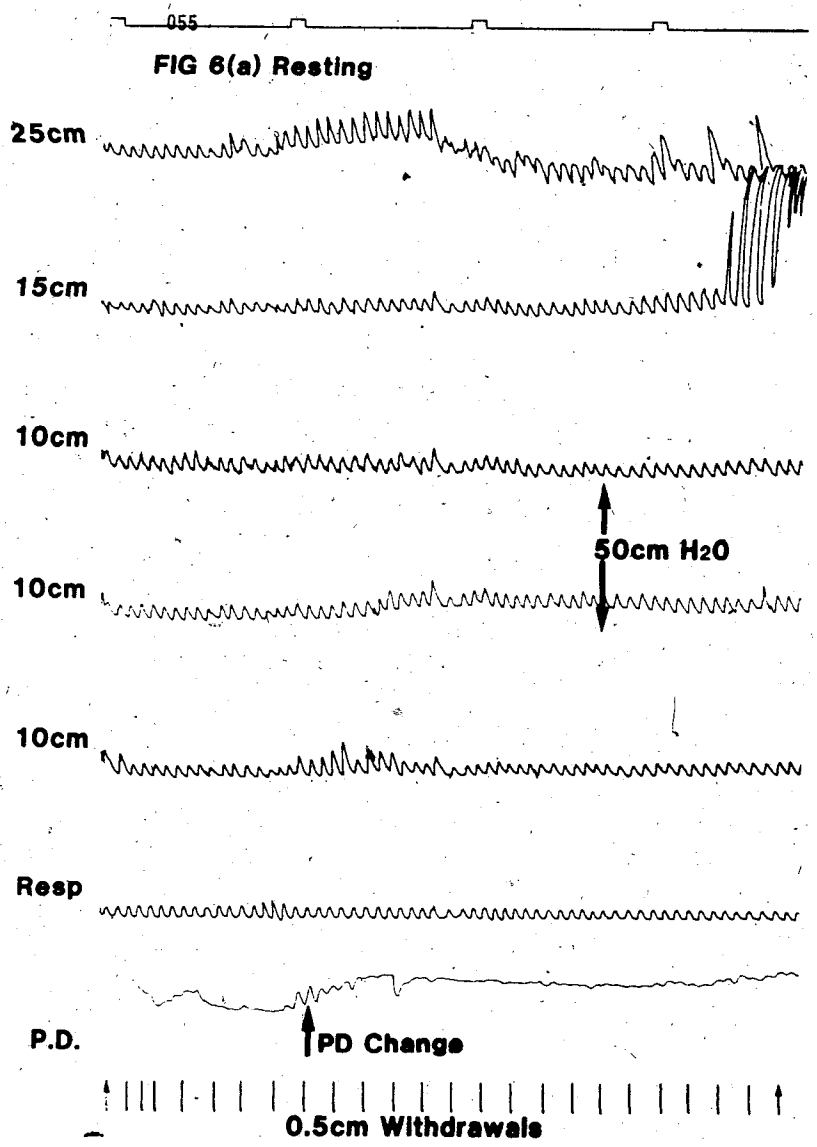


FIG 6(a) Resting

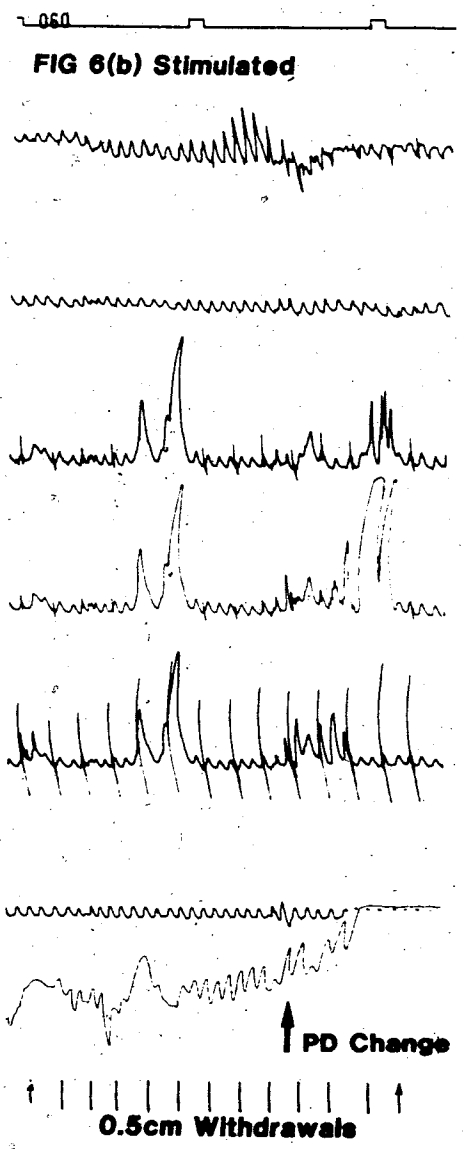


FIG 6(b) Stimulated

Figure 7: TOTAL AND INDIVIDUAL MEAN GASTRITIS SCORES PER AGE GROUP