Progress reports

Alkaline reflux gastritis: a critical reappraisal

Epigastric pain and bile vomiting as a sequel to the creation of a gastroenteric stoma form a vexing clinical problem as old as gastric surgery itself. In 1881, Woffler commented on this association in a patient who had undergone a gastroenterostomy and, shortly thereafter, Billroth reported a second case after a gastric resection. Seventy years later, Wells and Welbourn provided the first clear description of the relationship between these postgastrectomy symptoms and chronic intermittent obstruction of the afferent limb. Thereafter, the afferent loop syndrome was usually deemed responsible. In 1965, however, Toye and Alexander-Williams challenged this concept by reporting an intriguing single subject human experiment. A 56 year old man, who had suffered from bilious vomiting and epigastric pain for eight years after a gastrectomy with Billroth II reconstruction, developed acute cholecystitis. At the time of cholecystectomy (and with the patient’s consent) a catheter was placed into his completely patent afferent loop. Postoperatively, the duodenal content was collected and, when the patient was fully recovered, the afferent loop was perfused with either content or saline. In both the recumbent and upright positions, content (and content only) regularly and predictably reproduced the patient’s symptoms as soon as it gained access to the lumen of the residual stomach. In order to shunt duodenal content away from the gastric pouch, an isoperistaltic Henley loop was interposed between stomach and duodenum. Postoperatively, the patient was ‘delighted with the result’. Without specifically being named, a ‘new’ postgastrectomy ‘syndrome’ had been tentatively identified, its aetiology hinted at, and one approach to its surgical therapy outlined.

The ‘syndrome’ defined

Over the past 15 years, numerous series have appeared in the surgical literature which purport to define the ‘syndrome’ (now commonly referred to as ‘alkaline reflux gastritis’) and attempt to document the therapeutic efficacy of various remedial operative procedures. A review of 324 patients described in 10 of the largest and/or best conducted of these series (Table 1) discloses that the two most common presenting complaints were abdominal pain (89%) and vomiting (94%). The vomitus was described as bilious in 163 of the 262 patients (62%) in whom a description of its character was specifically noted, and symptoms of early postprandial dumping were present in 10% of these questioned in this regard.

Assessment of the residual stomach’s capacity to elaborate HCl was accomplished in 179 patients: 152 (84%) were said to show hypochlorhydria or achlorhydria – that is, ‘alkaline’ gastric content. Endoscopic ‘gastritis’ (usually defined as erythematous, oedematous, friable mucosa)
associated with bile ‘reflux’ was present in 262 of 276 patients who underwent gastroscopy. Histologic ‘gastritis’ (infrequently defined) was said to be shown in 123 of 155 patients who were biopsied, although the biopsy site was seldom specified. Fifty five per cent of patients queried had lost weight in variable amounts, and hypochromic microcytic anaemia was found in 48 of 185 patients tested. Most importantly, none of the patients was said to have evidence of recurrent ulcer, afferent or efferent loop obstruction, or cholelithiasis, findings which emphasise the exclusionary nature of the diagnosis.

A variety of previous operative procedures had been performed in the 313 patients for whom this information was provided (Table 2). Fifty five per cent of the patients had undergone gastric resection with restoration of gastrointestinal continuity as a BII gastroduodenostomy. Despite their widespread popularity in the operative treatment of peptic ulcer disease, truncal vagotomy and drainage were the index procedures in only 17% of these patients. Although no denominator figures are available, these data have been interpreted as indicating that resected patients, in general, and resected patients reconstructed via a BII, in particular, are most prone to the development of the ‘syndrome’. On the other hand, the addition of truncal vagotomy to resection appears to be of little consequence, as equivalent numbers of resected patients developed the ‘syndrome’ with and without concomitant vagus section (121 patients vs 114). In those patients in whom it was specified, the indication for the index operation was duodenal ulcer in 92 and gastric ulcer in 10, reflecting the relative prevalence of these two disease entities in the population as a whole. The interval between index operation and the onset of ‘typical’ symptoms was extremely variable, ranging from several weeks to more than 20 years. A similar variability has been noted with respect to recurrent ulcer disease and appears to be related, at least in part, to the type of initial procedure performed. Whether or not a similar relationship exists for the ‘syndrome’

Table 1  Symptoms and signs in 324 patients with diagnosis of ‘alkaline reflux gastritis’

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Endoscopic gastritis</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Histologic gastritis</td>
</tr>
<tr>
<td>Bilious vomiting</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Dumping</td>
<td>Anaemia</td>
</tr>
<tr>
<td>↓ H+</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Index operation in 313 patients with diagnosis of ‘alkaline reflux gastritis’

<table>
<thead>
<tr>
<th>Operation</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal gastrectomy with gastrojejunostomy</td>
<td>92 (55%)</td>
</tr>
<tr>
<td>Truncal vagotomy and antrectomy with gastrojejunostomy</td>
<td>81 (47%)</td>
</tr>
<tr>
<td>Subtotal gastrectomy with gastroduodenostomy</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Truncal vagotomy and antrectomy with gastroduodenostomy</td>
<td>40 (24%)</td>
</tr>
<tr>
<td>Truncal vagotomy and drainage</td>
<td>52 (17%)</td>
</tr>
<tr>
<td>Gastroenterostomy</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (8%)</td>
</tr>
</tbody>
</table>
under consideration cannot be ascertained from the data presented in the series reviewed.

These 324 cases undoubtedly represent but a small fraction of those patients diagnosed and operated upon. In fact, it has been stated that ‘alkaline reflux gastritis’ may be the most common of the recognised postgastrectomy disorders. This is unlikely. Assuming, first, that the ‘syndrome’ is a distinct clinical entity, and, second, that bile vomiting is an integral part of it, the 1974 report of Griffiths15 bears directly on this issue. Of 1311 patients undergoing operation for peptic ulcer disease seven to 18 years previously, 119 (9%) were found to have developed bile vomiting in the interim. In 87 of these, some convincing cause other than reflux was shown either radiographically or at operation, leaving 32 patients (3% of the total) who, by even the most liberal criteria, might have been afflicted with the ‘syndrome’. Parenthetically, it is for this reason that primary reconstruction via a Roux-en-Y limb after gastrectomy is inadvisable; the risk of marginal ulcer far outweighs any anticipated benefits.

In the series reviewed, a wide variety of operative procedures designed to shunt upper intestinal content away from the residual gastric pouch was used. Creation of a Roux-en-Y limb (length ranging from 10 cm to 80 cm) was the most popular (229 patients), followed by interposition of an isoperistaltic jejunal loop (42 patients). Although the results achieved may represent the expectation of the surgeon as much as the experience of the patient, they have been reported to be quite salutary: satisfactory to good in 79% after Roux-en-Y creation and in 81% after loop interposition. From these data, many surgeons have chosen to ignore the facts that the more recent (and more objective) of these series document a less impressive overall experience,6–9 and that the creation of a Roux-en-Y limb can in and of itself be associated with severe and prolonged delays in gastric emptying.16 They have accepted the existence of the ‘syndrome’ uncritically and have embraced its operative treatment enthusiastically.

The sceptics’ view

Critics remain unconvinced that the ‘syndrome’ is a distinct disease entity or, if it is, that its aetiology is in any way related to alkalinity, gastritis, or reflux.17 Such scepticism seems quite justified. In the first instance, no consensus exists in the series reviewed as to the exact nature of the symptomatic components supposedly specific to the ‘syndrome’. When described at all, the ‘typical’ pain has been noted to be intermittent, continuous, nocturnal, unrelated to meals, exacerbated by meals, worse in recumbency, unaffected by position, etc. Similarly, ‘typical’ vomiting has been described as postcibal, sporadic, nocturnal, containing food, not containing food, associated with pain, unrelated to pain, etc. In addition, one recent series6 has cogently emphasised the unpredictable, almost random, nature of the outcome when operation is undertaken on the basis of ‘typical’ symptoms alone.

Furthermore, preoperative documentation of these more objective indices, which are supposedly specific for the ‘syndrome’, is notably absent in most surgical series. Of the 324 patients reviewed, preoperative endoscopy was not performed in 48 (15%), preoperative acid output was not assessed in 145 (45%), and preoperative mucosal histology was not
evaluated in 169 (52%). Nor was postoperative reversal of any of these indices assessed in almost 80% of instances. Indeed, the English literature reports only 73 patients who underwent both preoperative and postoperative endoscopy; of these, 68 were said to have improved. Seventy two patients were rebiopsied; \(^6,\) \(^7,\) \(^13,\) \(^18-20\) of these, 25 showed 'improvement' in histologic gastritis. In 22 patients, preoperative and postoperative assessment of the capacity of the residual gastric pouch to secrete acid was accomplished; \(^7,\) \(^13,\) \(^20\) only four showed increased acid output. Finally, an attempt has been made to quantify (rather than simply to observe) preoperative and postoperative reflux in a mere 34 patients, \(^18-20\) all of whom improved in this regard. Most important, a cohort of asymptomatic postgastrectomy patients was not studied in any of the major series purporting to assess the syndrome, bringing to mind Meunch's law: 'nothing improves an innovation like lack of controls.'

**Four critical questions**

Because of these deficiencies, serious reservations have been expressed as to the postulated pathophysiology of the 'syndrome' and, indeed, as to its very existence. \(^17\) The issue is unlikely to be resolved until answers are obtained to four critical questions.

**Question 1**
Does exposure of proximal gastric mucosa to upper intestinal content result in the development of 'gastritis'?

A principal difficulty encountered in attempting to answer this question is that no uniform agreement exists in the literature as to the precise definition of 'gastritis'. This is especially true in terms of histology but is also true, although to a lesser extent, in terms of endoscopy. Furthermore, except for the diagnosis of atrophic gastritis, the correlation between what is noted endoscopically and what is seen pathologically is tenuous, at best.

At least two definitions of histologic gastritis have been used in those few clinical studies which have addressed the 'syndrome' by attempting to quantify reflux in some way. The Whitehead classification\(^21\) involves assessment, first, of whether or not the gastritis is superficial (inflammatory and reactive changes confined to the superficial epithelium) or atrophic (reduction in the number of gastric glands present), and, second, of whether or not the gastritis is active (numerous polymorphonuclear leucocytes in the lamina propria) or quiescent (negligible inflammatory infiltrate). These criteria were used in at least one study\(^18\) (perhaps also in a second\(^19\)) which quantified reflux by measuring intragastric bile acid content or concentration. In both, Roux-en-Y reconstruction resulted in a significant decrease in intragastric bile acids, but mucosal histology either did not change or actually worsened. In a third study,\(^22\) however, each of 11 'typically' symptomatic patients (all of whom had raised total bile acid concentration in their autologous intestinal content) did show gastritis by these criteria. In contrast, only two of eight asymptomatic patients showed any morphologic abnormality whatsoever.

A second definition has evolved from observations made in the experimental laboratory and is based on a study\(^23\) in which proximal acid peptic secreting mucosa was interposed in the form of a Heidenhain pouch.
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into the proximal jejunum. After six months of exposure to upper intestinal content, the pouch mucosa predictably developed (1) infiltration of the lamina propria with acute inflammatory cells; (2) increased numbers of mucus containing cells; (3) decreased numbers of parietal and zymogen cells; and (4) cystification and 'corkscrewing' of the glands. In contrast, pouch mucosa exposed to its own endogenous secretion remained histologically normal. Particularly pertinent to the clinical circumstance is the fact that all of these experimental alterations were significantly worsened in the absence of the antrum and its trophic hormone, gastrin. Variations of the same model have been used by several different investigators with the same result in almost every instance. Despite the fact that it is based exclusively on experimental data, this classification is, in my opinion, more relevant to the clinical question under consideration, because it has evolved from direct observation of the manner in which gastric mucosa responds when exposed for a prolonged period of time to upper intestinal content. Indeed, when these criteria were used, a recent clinical study of postgastrectomy patients was able to show a direct and significant correlation between recumbent and postprandial intragastric bile acid concentration and content and the severity of histologic gastritis in gastric biopsies obtained from a constant location away from the region of the gastroenteric anastomosis. Furthermore, when restudied six to 22 months later, all of those patients who had been converted to a Roux-en-Y limb because of statistically aberrant reflux patterns showed a significant decrease in the severity of gastritis, associated with significant recovery of their capacity to elaborate HCl in response to standard stimuli. Thus, both clinical and experimental evidence exists to support the proposition that exposure to upper intestinal content does result in quantifiable morphologic damage to proximal gastric mucosa. When applied to the 'syndrome' under consideration, more uniform agreement exists as to the definition of endoscopic gastritis: an erythematous, oedematous, and friable gastric mucosa involving more than the area surrounding the stoma itself. Mucosal hyperaemia is considered by many to be the most specific of these criteria, based on a study in which a significant correlation was found between hyperaemia and the concentration of bilirubin in samples of gastric juice obtained at endoscopy (a procedure which itself may, of course, alter reflux). Experimental support for this association does exist: when bile acids at low pH are applied topically to proximal gastric mucosa, hyperaemia, oedema, and friability rapidly ensue, probably as a consequence of increased mucosal blood flow. Unfortunately, only two clinical studies have directly addressed the relationship of reflux quantity to endoscopic gastritis. In one, hyperaemia was not used as a criterion; in the other, no correlation between this finding and intragastric bile acid concentration or content was found. Nevertheless, the almost uniform disappearance of erythema and oedema following the creation of a Roux-en-Y limb, coupled with the laboratory observation alluded to, indicates that the postulated relationship may be valid. The subjective nature of the assessment inevitably limits its usefulness as a diagnostic tool, however.

To summarise: the data suggest that the answer to the question under consideration is a tentative 'yes' with respect to histologic gastritis and an even more tentative 'perhaps' with respect to endoscopic gastritis.
QUESTION 2

What factors in upper intestinal content might be responsible for the development of gastritis? In a series of ingenious experiments, Delaney et al.25 chronically exposed acid-peptic mucosa to either pure bile, pure pancreatic juice, or whole jejunal content. All three preparations developed marked histologic gastritis, as defined above, but whole jejunal content caused more severe changes than did either pancreatic juice or bile, which were approximately equal. Therefore, several reasonable candidates, either alone or in combination, are available, although none can be implicated with certainty at the present time.

Considerable attention has been focused on the possible role of the bile acids. This is so for two reasons: first, under certain experimental conditions, the bile acids are acutely ulcerogenic in proximal gastric mucosa,33 and, second, they have the capacity to ‘disrupt’ the so called gastric mucosal barrier – that is, to render the mucosa incapable of maintaining intraluminal pH and electrical gradients.34 Because the precise anatomic location of the barrier is unclear, the mechanism of action of the bile acids is also unclear. Current evidence suggests, however, that their primary effect may be related to their detergent properties, which allow them to solubilise the lipid portion of the luminal oriented membrane of surface epithelial cells. This effect is apparently unrelated to their absorption by the mucosa.35–37 Bile acid species differ in their capacity to produce morphologic and electrochemical damage, depending on concentration, conjugation status, hydroxylation, and the ambient pH.36–41 This last factor may be the most critical, as, at low pH, only the taurine conjugates induce injury; the other conjugates precipitate. Conversely, at high pH (the situation which usually pertains after gastrectomy), the deconjugated and dihydroxy bile acids are more damaging than are the conjugated and trihydroxy bile acids. The minimal injurious concentration may also be a function of pH, as well as of the critical microcellular concentration of the individual bile acid species,36 although this last is uncertain. For these reasons, a variety of bile acids might be involved in the production of mucosal injury depending on the luminal environment of the moment.

A second factor in upper intestinal content with potential for damage is lysolecithin, the product of the intraduodenal hydrolysis of lecithin by pancreatic phospholipase A. Both lysolecithin and pancreatic phospholipase A have been recovered in greater than normal amounts from the intact stomachs of patients with active benign gastric ulcer disease,41 42 a condition in which gastritis is common.45 In addition, lysolecithin in sufficient concentration has been shown to increase gastric mucosal permeability to hydrogen ion44 45 and to induce acute ulceration in certain experimental models.46 Because bile acids both potentiate the production and inhibit the degradation of lysolecithin, the combination of the two may have a potential for injury which is far greater than that of either alone. Despite the apparent applicability of these experimental observations, it should be pointed out that neither the bile acids nor lysolecithin have been studied specifically for their capacity to produce a morphologic picture of gastritis similar to that observed in interposed pouches or in post-gastrectomy patients.
**QUESTION 3**

Is it possible that gastritis, per se, is in any way responsible for the 'typical' symptoms of the 'syndrome'? At best, the available information points to a potential association but falls far short of establishing cause and effect. The recent report of Warshaw,47 however, may apply in this regard. It was found that patients putatively suffering from the 'syndrome' developed 'typical' symptoms when challenged with an intragastric solution of concentrated NaOH, while control patients did not. These results raise the intriguing possibility that the presence of gastritis may render the mucosa uniquely susceptible to topically damaging agents.

**QUESTION 4**

Is there a relationship between 'excessive' enterogastric reflux and the symptomatic components of the 'syndrome'?

This question is, of course, central and critical to the controversy. Unfortunately, two fundamental difficulties present themselves in attempting to provide an answer. The first has already been touched upon – namely, the difficulty in deciding which symptoms are specific to the 'syndrome'. One reasonable approach to this problem is to identify either those symptoms which are ameliorated when reflux has been demonstrably eliminated in a quantitative way or, conversely, those symptoms which are predictably induced when endogenous upper intestinal content is instilled directly into the stomachs of 'typically' symptomatic patients. Only three studies have been reported which take this approach. In two,18 20 coincident with the elimination of reflux, continuous, mild, burning epigastric pain and bilious vomiting were also eliminated, while episodic nausea and vomiting decreased in frequency. Both of these studies used intragastric bile acid concentration and content as markers for reflux. In the third study,22 installation of intestinal content into the residual gastric pouch promptly produced burning epigastric pain coupled with nausea in 10 of 11 symptomatic patients, compared with only one of 10 control subjects. At a minimum, then, these are the only symptoms which could conceivably be related to reflux.

The second difficulty encountered relates to the precise meaning of the adjective 'excessive'. The term has several possible connotations: first, that gastric mucosa is exposed to intestinal content in greater than normal amounts (volume or concentration); second, that it is exposed to intestinal content which has an abnormal composition; or, third, that it is exposed to intestinal content for too long a period of time. Each of these possibilities has been addressed to a greater or lesser degree in one or more of those few studies in which reflux has been quantified in some way and in which a matched group of asymptomatic postgastrectomy patients has been simultaneously studied.18 20 22 32 48–50

The majority of these studies has chosen to define 'excessive' reflux as an increase in amount, measured either as an increase in intragastric bile acid concentration, as an increase in net bile acid reflux per unit time, or as an increase in reflux volume assessed by gamma scintigraphy after injection of 99Tc-labelled HIDA.20 32 48–50 Although consensus is not complete, the results of these studies hint that, if a relationship does exist between reflux and the syndrome, these indices may be the most appropriate discriminators between symptomatic and asymptomatic patients. On the
other hand, only three studies have directly examined the composition of reflux in any detail, and all confined themselves to an analysis of the individual bile acid species present. In two of these,\textsuperscript{20,22} in which a total of 17 asymptomatic and 25 symptomatic patients were evaluated, no marked difference could be detected between groups. The third report\textsuperscript{49} found a modest percentage of increase in the relative proportion of dihydroxy bile acids, particularly deoxycholate, in afflicted patients. Only three symptomatic and four control subjects were studied, however. Thus, the data base supporting this second definition of ‘excessive’ reflux seems somewhat feeble. Finally, only two studies\textsuperscript{20,32} have addressed the possibility (and then only indirectly) that ‘excessive’ reflux may relate to inadequate clearance of upper intestinal content from the gastric lumen. In both, no differences in scintographically determined gastric emptying of a solid meal were noted between symptomatic and asymptomatic postgastrectomy patients. Whether or not a similar circumstance pertains with respect to reflux \textit{per se} is unknown, so that, for the moment at least, this definition of ‘excessive’ reflux must be discarded simply for lack of information.

By focusing only on those symptoms potentially attributable to reflux and by defining ‘excessive’ reflux as an increase in amount, however measured, it is now possible to attempt to answer the clinical question posed. If a specific relationship between symptoms and reflux does, in fact, exist, that relationship must fulfil Koch’s postulates: (1) the symptom complex always occurs in the presence of excessive reflux; (2) the symptom complex never occurs in the absence of excessive reflux; (3) the symptom complex is eliminated by eliminating excessive reflux; and (4) the symptom complex is induced by inducing excessive reflux. How does ‘alkaline reflux gastritis’ fare in this regard?

First postulate: the symptom complex always occurs in the presence of excessive reflux. Four studies\textsuperscript{20,32,49,50} have used intragastric bile acid concentration as an index of the amount of reflux in afflicted patients and have contrasted the results obtained with those found in asymptomatic postgastrectomy controls. In three of these studies,\textsuperscript{20,32,50} net bile acid reflux was also determined. In one,\textsuperscript{50} raised values for fasting bile acid concentration and for net bile acid reflux per hour clearly separated seven symptomatic patients from an equal number of asymptomatic controls. Specifically, the finding of a net bile acid reflux of 120 \textmu M/h was said to be 100\% sensitive and 100\% specific for patients with epigastric pain coupled with ‘bile regurgitation’. Similarly, in a second study,\textsuperscript{20} all five patients with the principal complaints of epigastric pain and bilious vomiting showed significantly raised intragastric bile acid concentration and content both in recumbency and postprandially. In seven of nine patients whose epigastric pain was unassociated with bile vomiting, however, these same parameters were not significantly different from those observed in control subjects. In contrast with these reports, intragastric bile acid concentration was not found to differ between experimental and control subjects in two studies,\textsuperscript{32,49} and, in one of these, net reflux per hour was also not discriminatory. It should be noted that the total number of patients involved was small, and estimation of bile acid concentration was made using samples of gastric juice obtained at endoscopy, a technique which has been shown to be unreliable.\textsuperscript{18} A fifth study evaluated bile acid
concentration in upper intestinal content rather than in gastric juice.22 Significantly higher fasting levels were found in the intestinal aspirates of all symptomatic patients, although it was not shown that this material actually refluxed. Finally, in a sixth study,48 using direct, radioisotopic assessment of reflux volume (probably the gold standard), the ‘entero-gastric reflux index’ of symptomatic patients (86±7%) was significantly greater than that of the controls (25±5%). Although these data do not prove the point, they suggest that the postulate under consideration may have validity.

Second postulate: the symptom complex never occurs in the absence of excessive reflux. The evidence for and against this postulate is essentially the converse of the evidence for and against the first. Two points concerning both require re-emphasis, however. First, in my experience,20 many patients with postgastrectomy complaints do not show statistically abnormal reflux patterns when compared with controls. Measurement of intragastric bile acid concentration and content is discriminate (78% specific, 100% sensitive) only for those patients who manifest the concomitant stomachs of epigastric pain and bile vomiting. These objective indices lose their value if other symptoms and signs are attributed to reflux. Second, it has been convincingly shown that, when estimated as intragastric bile acid concentration, the amount of reflux is not constant, even in the fasting state. Variations can be considerable, especially with respect to the time of day (greatest at night, less during the day hours).19 Therefore, to be of value, the conditions under which the assessment of reflux is made using this marker must be rigidly standardised between control and experimental subjects.

Third postulate: the symptom complex is eliminated by eliminating reflux. At first glance, the near universal claims of symptomatic success after diversionary procedures, particularly those of the early surgical series, would seem to present an irrefutable argument in favour of this postulate. Because none of these studies assessed reflux in a quantitative way, however, because of the recent appearance of less enthusiastic and more objective reports,6 9 and because a placebo effect of operation can never be entirely eliminated from this type of analysis, these data must be viewed with considerable circumspection. In fact, only three studies have attempted to assess the therapeutic efficacy of operation in relation to alterations in the amount of reflux achieved by the procedure.18–20 In one,19 a five- to 13-fold decrease in intragastric bile acid concentration resulted in partial symptomatic improvement in 12 of 13 patients. The specific symptoms ameliorated were not identified, however. A second study20 clearly showed that a 45 cm Roux-en-Y limb completely eliminated reflux of bile acids and that, concomitantly, epigastric pain and bilious vomiting were abolished. In the third study,18 a Roux-en-Y limb of similar length reduced net bile acid reflux/hour to less than 120 μM in 16 subjects. Ten of the 11 who had shown preoperatively a net reflux per hour greater than this amount experienced marked symptomatic improvement, as compared with only one patient of the five with a preoperative value less than that amount. It requires re-emphasis that the only symptoms regularly affected in this study were those of mild continuous epigastric pain, bile regurgitation, and bilious vomiting. The meagre quantitative data available suggest that, for these specific symptoms at least, the postulate under
consideration may have validity.

Fourth postulate: the symptom complex is induced by inducing excessive reflux. This postulate represents the very crux of the issue. It is surprising, therefore, that only one published report has directly addressed the question of whether or not autologous intestinal content from ‘typically’ symptomatic patients is capable of reproducing ‘typical’ symptoms. In that study, upper intestinal content was obtained from 21 postoperative patients following the intravenous administration of CCK-OP. Eleven of these patients complained of abdominal pain, bilious vomiting, and nausea. The 10 remaining patients were asymptomatic postoperative controls. No patient showed any radiographic abnormality of the upper gastrointestinal tract or gall bladder. Analysis of the bile acid profiles of both groups revealed significantly greater total bile acid concentrations in the intestinal content of the former, although the relative proportions of bile acid species present were not different from those observed in the latter. Both autologous content and normal saline were then instilled in a double blind fashion into the residual stomachs of the control and experimental subjects. With content, 10 of the 11 symptomatic patients developed abdominal pain and nausea, whereas instillation of normal saline elicited no response. On the other hand, when autologous content was instilled into the intact stomachs of asymptomatic controls, only two of the 10 developed symptoms and, in both, normal saline also evoked a response. The value of this report would have been magnified if an attempt had been made to incorporate a crossover design into the study (instilling content from symptomatic patients into asymptomatic ones and vice versa). The results achieved with this manoeuvre might have provided an important clue as to the relative importance of an abnormal ‘reflux’ content as opposed to an ‘abnormal’ mucus membrane in the genesis of these particular symptoms.

The study also addressed the possible role of the bile acids themselves in this regard, by instilling into the stomachs of both groups an artificial bile acid solution with a composition similar to that observed in the symptomatic patients. None of the asymptomatic patients and only one of the symptomatic patients responded. It would appear, then, that the bile acids are not central to the aetiology of the symptomatic components of the ‘syndrome’, a fact which, if true, would explain the observation that cholestyramine, a bile salt binding resin, is ineffective in relieving symptoms when given in the usual way. It is, of course, unfortunate that the symptom provoking intestinal content was not analysed for other potentially damaging agents, particularly lysolecithin. Nevertheless, with specific respect to the postulate under consideration, this single report suggests that it too may have validity.

To summarise: it is not possible to provide an unequivocally affirmative answer to the central clinical question under consideration. This is so primarily because the quantitative data base available to affirm or deny a relationship between reflux and symptomatology is neither broad nor deep. When evaluated critically in terms of Koch’s postulates, however, the information for each is sufficiently compelling to suggest that the existence of the syndrome, as well as the postulated primacy of reflux to it, should not be dismissed out of hand. Without doubt, the ‘syndrome’ has been overdiagnosed, the symptoms generally ascribed to reflux have been
uncritically defined, and objective indices of reflux have been sought all too infrequently. Nevertheless, it is difficult either to ignore what few objective data are available or to discount completely the widespread clinical impression that a substantial number of patients have been subjectively and objectively improved by remedial operation.

In my opinion, three general conditions must be fulfilled before the diagnosis can be rendered scientifically acceptable and therefore clinically useful. First, the data base for each of the postulates pertaining to the critical questions discussed, especially the last, must be expanded. Second, the precise aetiologic factors responsible for both gastritis and symptoms must be clearly identified. Finally, rigorous diagnostic criteria must be developed from this information which are so specific and sensitive that a successful therapeutic outcome becomes predictable and reproducible rather than random and haphazard.

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