Gastrin, acid, and bile

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Bile in the stomach has been suspect for some time in connexion with the processes of gastritis and even gastric ulcer. James and Pickering (1949), inspecting night aspirates, found bile in the stomach of 70% of gastric ulcer patients and in 30% of duodenal ulcer patients.

Siurala and Tawast (1956) studied 366 patients by gastroscopy, gastric biopsy, and by measuring the surface tension of the resting stomach juice. By these means they observed that surface tension-lowering agents, presumed to be from bile, were more general in cases of gastric atrophy and in resting juice with a high pH.

DuPlessis (1962; 1965) in two studies decided that gastritis in 93 specimens resected from gastric and duodenal ulcer patients 'might be' due to pyloric reflux, and after gastrectomy and gastrojejunostomy gastritis, ulcer, and even carcinoma might be associated with the backflow of duodenal juice that these operations allow.

Capper, Butler, and Buckler (1966) and Capper, Airth, and Kilby (1966), also in two series of patients, measured the alkaline area of stomachs at operation after Billroth and Polya resections, and watched pyloric regurgitation radiologically in a variety of patients. Their conclusions were that gastritis and alkaline areas evolved 'where duodenal fluid ran over gastric mucosa', and that pyloric reflux was much more common in gastric ulcer patients and achlorhydric than in duodenal ulcer patients or normal people. These records incline one to accept a relationship between low acid, gastritis, and pyloric regurgitation.

Experiments in rats (Sander, Myren, and Hel-singen, 1964) and dogs (Byers and Jordan, 1962; Belowski, 1962) have failed to show degeneration of gastric mucosa after placing it in contact with gallbladder bile or duodenal juice. In conflict with these results has been the finding by Lawson (1964) that a 2 cm marginal area of atrophic gastritis followed the various operations in dogs in which duodenal juice was allowed to be in contact with stomach lining; Roux anastomosis prevented these changes.

MATERIALS AND METHODS

In 413 consecutive patients, quarter-hourly collections of stomach juice were inspected for obvious bile before and after stimulation by pentagastrin 6 µg/kg. In 100 of these, bilirubin was measured in all samples. These patients were placed in three groups: those with maximal acid responses below 10 m-equiv/hr, between 10 and 35 m-equiv, and over 35 m-equiv. For convenience these patients are called low, medium, and high secretors: it is known that the low-secreting groups are suffering some degree of diffuse gastritis (Christiansen and Johansen, 1966).

In 10 patients, 10 days after cholecystectomy, and with normal liver function tests, bile was collected from a T tube at 2 lb suction for an hour before and after pentagastrin 6 µg/kg and its volume and the concentration of bilirubin were assessed. These patients had fasted for 15 hours before the test.

Nine patients having cholecystograms had the gall bladder shadow measured in the antero-posterior plane just before and half an hour after pentagastrin 6 µg/kg. The patients were in the same position for both films, and shadows were measured in square millimetres.

MEASUREMENT OF BILIRUBIN This has been done using the colour change in the diazo reaction, measured at 578 mµ, on a Unicam SP.600 spectrophotometer (Jendrassik and Grof, 1938). This test has given variations of 1% in the bilirubin ranges from 0.1 to 2.5 mg %: down to 0.01 mg % readings varied up to 6%, this being the limit of the scale.

Errors from different opacities of the stomach juice are allowed for by using as a control part of the sample under test. This was checked by diluting known concentrations of bilirubin in standard amounts of random samples of stomach juice not containing bile; bilirubin readings were not affected by a great variety of opacities. Varying the pH from 1 to 10 also had no effect on bilirubin readings. The test is thus reliable in the ranges used in this study.

RESULTS

In the 413 patients having pentagastrin tests, the incidence of observed bile in quarter-hour samples rose from 46% while fasting to 60% after stimulation. Measuring the amount of bilirubin and its

TABLE I

CHANGES IN BILIRUBIN IN STOMACH JUICE AFTER PENTAGASTRIN IN 100 PATIENTS RELATED TO MAXIMUM ACID SECRETORY RESPONSE

No. of Patients	Maximum Acid (m-equiv/hr)	Total Bilirubin (mg)		Maximum Bilirubin Concentration (mg %)	
		One-hour Basal	One-hour Stimulated	Basal	Stimulated
25	-10	73.74	98.32	2.466	1.775
50	10-35	17.28	39.22	0.356	0.558
25	35+	15.78	58.65	0.271	0.595

concentration in 100 of these patients uncovered these trends (Table I). In resting juice, medium and high secretors had small amounts of bilirubin at low concentrations. Compared with this, low secretors had four times as much bilirubin ($P < 0.02$) at eight times the concentration ($P < 0.05$). After stimulation with pentagastrin, bilirubin of the same concentration and amount was found in the stomach in all the patients. There was (1) trebling of the amount in medium and high secretors ($P < 0.05$), and (2) considerable lowering of the concentration in the low secretors ($P < 0.01$).

EFFECT OF PENTAGASTRIN ON BILIARY FLOW In 10 patients tested, there was a 41% rise in the amount of bile collected from the T tube ($P < 0.02$), and a 33% rise in its concentration of bilirubin ($P < 0.01$), which accounts for a total rise of 88% in the quantity of bilirubin leaving the liver after stimulation by pentagastrin (Table II).

TABLE II

CHANGES IN T TUBE BILE AFTER PENTAGASTRIN IN 10 PATIENTS

	T-tube Bile	
	One-hour Basal	One-hour Stimulated
Mean vol. (ml)	19.35	27.38
Bilirubin (mg %)	29.97	39.74

EFFECT OF PENTAGASTRIN ON GALL BLADDER SIZE In nine patients tested, the mean size of the gall bladder was unchanged half an hour after injection of pentagastrin ($P < 0.9$). No notable action of gastrin on the gall bladder can be argued from this.

There are thus three important findings from these studies: (1) pentagastrin given to 75 patients able to secrete more than 10 m-equiv of acid under maximal stimulation caused more bilirubin to appear more often at higher concentration in the stomach than at rest. (2) But, the 25 patients unable to secrete more than 10 m-equiv acid had more bilirubin in the stomach at rest, at a much higher concentration;

they answered stimulation with a hardly noticeable rise in amount and a consistent fall in concentration.

Pentagastrin caused an 88% rise in quantity and 33% rise in concentration in bile collected in a T tube.

DISCUSSION

In all the series of figures for bilirubin, there was a vast range, from zero to several hundred milligrams for total bilirubin, and into the teens for concentrations. This has clouded the probability figures; at least three forces here worked against an even and statistically concise set of results.

These were unselected patients coming to a routine maximum acid testing service; they all had some indisposition of the digestive system, so that none could be stated to be normal. We were observing a heterogeneous group of diseases, from pyloric stenosis to malabsorption, with many patients undiagnosed at the time of testing.

Stomach tubes have been blamed for causing pyloric incompetence, either in association with nausea, or by their contact with the antral mucosa provoking a backflow of bile like that seen through the much quoted gastrostomy of Alexis St. Martin. There is no final evidence about either of these accusations, but one of us has tested in five dogs the effect of a stomach tube on pyloric incompetence; observed for 15 minutes after intubation, none of these showed biliary backflow into the stomach. These findings place some doubt on the importance of intubation distorting the figures for bile in the tests recorded here.

A major unknown factor is the state of the sphincter of Oddi, which might by prolonged contraction account for the many negative results for bile in the series. It is known (Ono, 1967) that the action of the sphincter of Oddi is independent of normal duodenal activity, and it is therefore a variable that cannot be accounted for at present.

In spite of these uncertainties, the probability values do confirm the two main trends seen in this study: (1) that bilirubin is much more concentrated

in the resting juice of low acid secretors (this is in harmony with the many other scrutinies of this subject), and (2) that pentagastrin in medium and high secretors allows a marked backflow of bile into the stomach; this was a threefold increase, more than can be explained solely by the 88% rise in bilirubin levels in T tube bile. The backflow could follow different phasing of duodenal and antral concentrations, increased force on the duodenal side without any change in the habit of the sphincter, or relaxation of the sphincter during duodenal contraction. It is impossible to describe details of the mechanism accurately at this stage, but the above findings suggest that there is an efficient barrier between the duodenum and antrum at rest in medium and high secretors, and that this barrier is to some extent breached, allowing retrograde flow, after pentagastrin stimulation. Disorganization of this partition mechanism is present in patients only able to secrete a small quantity of acid under maximum stimulation.

The reason for the bile backflow after stimulation is not clear; it could be purposeful to some end not yet understood, or it might be an unwelcome but unavoidable byproduct of the general motor and secretor responses to stimulation. Certainly two things add weight to the latter idea: first, any bile coming into the stomach soon after a normal meal will find itself mixed with, and possibly adsorbed onto, semi-solid food and a variety of liquids; its concentration at the mucosa will be a great deal less than that recorded in these tests in empty stomachs, and possibly insignificant. Second, the resistance to this backflow at rest must be to some purpose; it is only in a fasting or near fasting stomach that a high concentration can reach the stomach lining for any length of time, and this is the point where its entry is resisted. Bile salts are known to damage oesophageal mucosa severely, and though their effect on stomach mucosa is less certain, the size of the massive muscle ring at the pylorus suggests that as well as taking part in the antral pump mixing machinery, it might be called on to separate the duodenum from the stomach at rest.

SUMMARY

In 413 patients having pentagastrin tests, there was, after stimulation, a rise from 46 to 60% in the number of quarter-hourly samples containing bile.

In 100 patients, bilirubin in stomach juice was measured before and after pentagastrin; these figures showed that in persons able to secrete more than 10 m-equiv HCl, stimulation caused backflow of bile into the stomach, and persons secreting less than 10 m-equiv HCl were unable to keep bile out of the stomach at rest.

Pentagastrin augments by 33% the concentration of bilirubin and by 41% the volume of bile leaving the liver.

From this study, pentagastrin does not cause an obvious contraction of the gallbladder.

One of us (G.J.C.) was supported by a fellowship from the Royal Victoria Hospital.

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