Vanishing Pancreatic Calcification


Pancreatic calcification is present in 75%-90% of patients with alcoholic chronic pancreatitis (CP) of long duration. Although it is believed to be closely associated with pancreatic dysfunction, the natural history of calcification in these patients is not known. In the present study, the authors investigated the course of pancreatic calcification in patients with CP in a prospective, longitudinal manner over a 23 year period. All patients were studied at regular intervals and details of etiology, clinical findings, pancreatic functions and any surgical procedure done were carefully recorded. Pancreatic calcification was assessed by a series of three X-ray films (2 oblique and 1 prone) centered on the pancreas. One hundred and seven patients with radiologically documented pancreatic calcification were studied. Eighty four patients had alcoholic chronic pancreatitis (group A) and twenty three had non-alcoholic chronic pancreatitis (group B). The mean duration of calcification was 10 and 12.6 years in groups A and B respectively.

Four hundred and seventy two film series of group A and 142 film series of group B were reviewed independently by two expert teams. Pancreatic calcification (amount, density and distribution) was estimated semi-quantitatively and graded according to a score system. The overall change in degree of calcification in an individual patient was classified as increase (or decrease) if the two teams noted a concordant and consistent change of at least one grade over a period of 3 yr in two or more film series. The patients were divided into three classes: phase 1 (increase in calcification), phase 2 (stationary calcification) and phase 3 (decrease in calcification). The majority of patients in both the groups initially showed an increase or extension of calcification (phase 1). Both the groups then passed into phases 2 and 3. During the observation period, 50% of patients in both groups had stationary pancreatic calcification (phase 2) and about one third showed a decrease in calcification (phase 3). Almost complete dissolution of stones was noted in 12 cases in the alcoholic and two cases in the non-alcoholic group.

Phases 2 and 3 were associated with longer duration of disease and more severe pancreatic exocrine and endocrine dysfunction. A total of 31 patients in both the groups had a ductal drainage procedure. A higher number of patients (21; 65%) with such a drainage procedure showed a decrease in calcification in contrast to patients who had undergone a cyst drainage procedure (5 of 17; 29%). This dissolution of pancreatic stones was probably related to duration of chronic pancreatitis and occurred frequently but not exclusively in patients with ductal drainage procedures. The authors feel that spontaneous dissolution of pancreatic stones is a rather common biological phenomenon in patients with chronic pancreatitis. The findings responsible for the dissolution, however, are not yet well understood.

Comment: The pathogenesis of pancreatic calcification in chronic pancreatitis is not clear but it has a close association with severity of pancreatic exocrine and endocrine dysfunction. In the presence of complications like pancreatic cancer (Ann Int Med 1968: 69: 66-70) or pseudocyst (JAMA 1944; 129: 1395-7). In a few cases there has been no obvious cause, and probably these are examples of spontaneous dissolution (Gastroenterology 1983: 84: 268-74). The calcification disappears in some patients is thus convincingly shown. What remains to be explained is its mechanism.

The decrease in the pancreatic calcification in the present study was related to increasing duration of disease, and was more frequent after ductal drainage procedures. The role of this phenomenon in pancreatic lithiasis is not established. It is likely to have some impact on current postulation about the pathogenesis of pancreatic stones. Theoretically an imbalance between promoting and inhibitory factors of lithogenesis may determine the progress of pancreatic calcification. Pancreatic stones are composed primarily of calcium carbonate in the form of calcite and vaterite (Dig Dis Sci 1986; 31: 476-80). Recent studies indicate that stone formation in CP is related primarily to two factors: (a) Acidification of the pancreatic juice and (b) changes in the composition of the pancreatic secretions, the latter with respect to the concentration of bicarbonate ions. The role of the bicarbonate ions in the formation of pancreatic stones has been reemphasized and a correlation between the concentration of bicarbonate ions and the incidence of stone formation is present. The authors suggest that the low pH of the pancreatic juice in patients with chronic pancreatitis is another important factor in the dissolution of pancreatic stones. It has been shown that the concentration of bicarbonate ions is inversely related to the concentration of calcium ions in the pancreatic juice. It is possible that the low pH of the pancreatic juice in patients with chronic pancreatitis may reduce the concentration of bicarbonate ions and, therefore, the solubility of calcium carbonate. This may lead to the formation of calcium carbonate stones, which may be more susceptible to dissolution. The authors recommend further studies to confirm these findings and to elucidate the mechanisms involved in the dissolution of pancreatic stones.
advanced stage of disease. This suggests that it may be a cofactor in promoting lithogenesis only in the early stages of disease.

Finally what is the relevance of this observation? It is worthwhile to note that with increasing pancreatic calcification pancreatic functions do not improve. Secondly, this observation will have an impact on the nomenclature of pancreatitis. Some cases labeled as chronic pancreatitis may indeed be cases of postcholecystectomy pancreatitis. Also while interpreting the results of treatment with various agents like oral tolbutamide (Gastroenterology 1987; 91: 900) or citrate (Gastroenterol Clin Biol 1979; 3: 615-20) for dissolution of pancreatic stones, the possibility of spontaneous dissolution needs to be kept in mind.

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A High Uterine Recurrence Following HSV; Will Division of the Right Gastroepiploic Bundle Help?


Intraoperative cobra red testing following highly selective vagotomy (HSV) shows persistence of acid secretion along the greater curvature of the stomach. This secretion, however, disappears immediately after division of the right gastroepiploic neurovascular bundle. In these patients, nerve cells have been localized in the dorsal motor nucleus of the vagus nerve (dmm X) which project preganglionic effector vagus nerve fibers to the greater curvature of the stomach. Although it is clear that these fibers are contained within the vagus nerve trunks, their intra-abdominal pathways are unknown. An axonal tracing method has been used to verify the hypothesis that the right gastroepiploic neurovascular pedicle contains these effector fibers from the dmm X. Fluorogold, a retrograde axonal tracer, enters the axoplasm of nerves by endocytosis; from there it is transmitted to the cell bodies of the neurons by axonal flow. Interruption of the axonal connection leads to failure of labeling of the cells from which the axon originates.

Twenty four anesthetized Sprague-Dawley rats weighing between 350 and 450 g were used for the study. Rats were divided into seven groups: groups 1 to 4—study groups, groups 5 to 7—control groups. Rats in groups 1 (n = 5) and 2 (n = 4) underwent anterior and posterior pyloroplasty respectively. Three rats (group 3) underwent both, anterior plus posterior pyloroplasty. The anterior nerve of Latarjet was divided in three rats (group 4). Division of the posterior nerve of Latarjet in rats is technically difficult, and the inclusion in the study of such a group was not considered feasible. The right gastroepiploic pedicle was injected with 20 μg of 57m fluorescent dye in all these groups. The right gastroepiploic pedicle was injected similarly in five rats without any additional surgical procedure (group 5). One ml of 0.04% fluorescent dye was injected into the femoral vein of rats in group 6, and group 7 rats did not undergo any surgery nor receive any fluorescent injection. In all the groups, brains were harvested and their frontal sections were examined by fluorescence microscopy. A three dimensional reconstruction of the distribution of the labeled nerve cells in the dmm X was made for each group. Of the control groups, no labeling of brainstem cells was noted in groups 6 and 7, whereas in group 5, an equal number of cells were found labelled on either side of the midline. Thus only when the tracer was introduced into the axons there was labeling of cells in the dmm X. No labeling was noted when it was injected into the femoral vein. In the study groups, after anterior pyloroplasty (group 1) or division of the anterior nerve of Latarjet (group 4), significantly less neurons in the left dmm X were found labelled. After posterior pyloroplasty (group 2), significantly lesser neurons were found labelled on the right side. No neurons were found labelled in the dmm X after anterior plus posterior pyloroplasty (group 3). The authors conclude that complete denervation of the acid secreting mucosa along the greater curvature during HSV is possible only if the right gastroepiploic neurovascular bundle is also interrupted.

Comment: Currently, HSV is considered by many workers as the operation of choice for uncomplicated duodenal ulcer (Am Surg 1987; 205: 542-7; Gut 1987; 28: 547). In this operation there is a round physiological balance (Br J Surg 1969; 58: 426; Gastroenterol 1970; 59: 522-7). The morbidity and mortality are also less than the other forms of ulcer surgery. However, the high recurrence rate of 39% on long term follow up has dampened the enthusiasm of many surgeons for this operation (Br J Surg 1974; 61: 1058-9). It is known that in 50% to 50% of cases with ulcer recurrence, the recurrence occurs within the first five years of surgery (Am Surg 1989; 205: 40-5). Even though immediate postoperative tests for completeness of vagotomy show adequate denervation of parietal cells, significant return of acid secretion has been noted on follow up in many patients (Dig Dis Sci 1981; 26: 824-7). The reason for this is not very clear. Attempts to reduce the high rate of ulcer recurrence after HSV have not met with much success.

The present paper demonstrates that the medial portion of the dmm X, which is responsible for gastric acid secretion (Am J Physiol 1987; 252: R 13-25), projects preganglionic effector fibers over the greater curvature to supply the parietal cells. Early postoperative conversion to a positive Hollander's test could be related to a persistent parietal cell hyperplasia by this pathway. Indeed, Demetri et al (Am J Surg 1987; 153: 249-53), who carried out intraoperative cobra red testing following HSV, demonstrated a significant persistant acid secretion along the greater curvature of the stomach, which disappeared after the sectioning of the right gastroepiploic pedicle. It is thus important that along with HSV, there should be denervation of the parietal cells controlled by this pathway. Theoretically, this can be achieved by adding to HSV either a combined anterior and posterior pyloroplasty or division of the right gastroepiploic pedicle. Conventionally an anterior wall pyloroplasty alone is done. Thus HSV plus pyloroplasty will still leave an intact vagal supply through the posterior wall of the pylorus. A prospective randomized trial of HSV plus pyloroplasty versus HSV alone on 100 patients followed up for three years failed to show any decrease in the rate of ulcer recurrence with the addition of a pyloroplasty (Br J Surg 1977; 2: 853-6). In another prospective trial, 100 patients were randomly selected to have either HSV alone, HSV plus pyloroplasty or selective vagotomy plus pylor-
injection of contrast medium, a puncture was made perpendicular to the cyst towards its centre. The localisation was done with the help of high definition fluoroscopy. After diathermic puncture, the cyst was injected with contrast medium through the same needle. Thereafter, a 10 F catheter was passed over the needle into the cyst. This catheter was then pushed into the cyst, the needle was pulled out and replaced by a sphincterotome to enlarge the cystoenterostomy up to 8 mm for the duodenum and 10 mm for the stomach. The cut was made by coagulating current and then a nasogastric catheter was placed. After ECD, the catheter was perfused with normal saline and left in place until complete regression of the cyst was achieved. After ECG, drainage of the cyst was usually performed with intermittent clearing of the pseudocyst. At follow-up visits, besides clinical evaluation, ultrasound examination was done in every patient and some patients underwent a repeat ERCP as well.

ECD was successful in 21 (96%) of 22 cases. Pain disappeared in 20 of 21 cases and symptoms of duodenal obstruction and cholelithiasis were relieved in all the patients. Only one patient who continued to have pain underwent pancreaticojunostomy. No complication was encountered in any patient. On follow up (mean period 31 mo, range 3-84), only 9% of patients had recurrence of pseudocyst. The success rate for ECG was 100%. Complications (gastric hemorrhage and pseudocyst infection) occurred in two patients and 19% had recurrence of pseudocyst. The authors concluded that ECD was an effective and definitive treatment in 19 of 22 cases and ECG in 8 of 11 cases. If these procedures are done in suitably selected patients, ECD should be the treatment of choice for paracolic cysts, whereas ECG is an alternative procedure for the drainage of retrogastric pseudocysts offering results comparable to percutaneous drainage.

Comment: Although it is difficult to predict the natural history of pseudocysts, in an individual patient, spontaneous resolution is very uncommon if the duration of cyst is more than 6 weeks. In one study, where patients were evaluated by serial clinical and ultrasonographic examination, spontaneous resolution occurred in 10 (40%) of 24 patients who had pseudocysts of less than 6 weeks' duration (Ann Surg 1986: 153: 609-12). Only one of 13 pseudocysts of 7-12 weeks' duration and none of the 17 pseudocysts of more than 13 weeks' duration resolved spontaneously. Further, pseudocysts persisting for more than 6 weeks have a high incidence of complications (Br J Surg 1975: 62: 174-82). Thus, it is not advisable to wait for spontaneous resolution of a cyst if it is more than 6 weeks old.

What is the best method of treatment of a pseudocyst? This has been a subject of controversy and several approaches have been advocated. Currently preferred treatments are: (i) surgical cystoenterostomy, (ii) US or CT guided percutaneous aspiration or drainage of the cyst, and (iii) endoscopic cystoenterostomy. Surgical cystoenterostomy is still considered by many as the most appropriate treatment (Ann Surg 1981: 143: 547-57, Surg Gynec Obstet 1981: 152: 809-12). The outcome of surgery depends upon the size and site of the cyst. The results of surgery are better if the cyst has a diameter of less than 5 cm and if it is filled with clear fluid. If the cyst has a solid component, the results are less favorable. If the cyst has a solid component, the results are less favorable. If the cyst has a solid component, the results are less favorable.

It is still a matter of debate whether cystoenterostomy is superior to endoscopic treatment. The former is associated with a higher incidence of complications and is more invasive. The latter is associated with a lower incidence of complications and is less invasive. However, the choice of treatment depends upon the patient's clinical status and the size and site of the cyst. If the cyst is small and located in the head of the pancreas, surgical cystoenterostomy is the preferred treatment. If the cyst is large and located in the body or tail of the pancreas, endoscopic treatment is the preferred treatment. If the cyst is intermediate in size and location, a combination of surgery and endoscopy may be necessary.
and a mortality of about 11 percent (Al J Strom 1978; 133; 190-201).
For this reason, nonsurgical methods have been gaining popularity. The aim of alternative treatment is not only to decrease the complications, but also to avoid or at least postpone surgery to an absolute indication. Such a treatment, however, must be a tolerable compromise without compromising further surgery in case of its failure.

US guided simple aspiration of pseudocysts has been attempted by many authors (Gastroenterol Radiol 1984: 5: 235-7, Radiology 1985: 157: 325-40, AJR 1986; 147: 1007-9). As this has been followed by a high relapse rate in most of the studies, this must be considered only a temporary treatment. Although multiple aspirations have been successfully performed, the discomfort associated with repeated punctures and the possibility of infection cannot be ignored. Several workers have therefore used certain drainage systems to relieve the cystic condition, but without complication associated with repeated punctures and the possibility of infection cannot be ignored. Several workers have therefore used certain drainages to relieve the cystic condition, but without complication. This technique, however, also has some limitations. It is suitable for large noncommunicating pseudocysts; paraduodenal cysts which are usually smaller in size are not easy to puncture and are not large enough to allow the catheter to curl up in the lumen. There is also significant risk of pancreatitis in patients with pancreatic pseudocysts, EGD and ECG both have been found to have a high success rate and the relapse rate of pseudocyst is relatively low. If these observations are confirmed by others, then this may provide a significant reduction in the need for surgery in these patients.

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Mechanism of Action of E coli Heat Stable Enterotoxin
Haust PX, Liu W, McRoberts JA, et al. (Division of Gastroenterology, Department of Medicine, University of California at San Diego Medical Center, and Division of Digestive Diseases, Department of Internal Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio, USA). Mechanism of action of Escherichia coli heat stable enterotoxin in a human colonic cell line, J Clin Invest 1988; 82: 514-23.

Heat stable enterotoxin (ST) of enterotoxin Escherichia coli (ETEC) causes secretory diarrhea by increasing the cellular cGMP levels. However, the mechanism by which cGMP stimulates intestinal secretion of electrolytes and fluids is not known. In the present study the authors have carried out in vitro experiments to investigate the mechanism of action of ST in a human colonic cell line. A cultured human colonic cell line (Tg4) derived from a large metastases of a human colon carcinoma, was used as a model system to study the colonic secretion. Tg4 monolayers were mounted between two fluid filled reservoirs (using chambers) that allowed active transport mechanisms to occur unimpaired while eliminating passive forces that might confound the observed differences. Permeability (PD) across the cell monolayers was measured by calomel electrodes and monitored with a potentiometer. This PD has been shown to result from transepithelial secretion of chloride ions; these are the only ions transported transcellularly by Tg4 cells. The short circuit current (Isc) needed to nullify the electrical PD indicated net Cl- secretion. When the ST was applied to the mucosal side of cell monolayers, an immediate increase in Isc was noted which plateaued after 30 min and then remained near maximal throughout the study period. The Cl- secretion (Isc response) in response to ST was dose-dependent. Both secretion to stimulated vesicles and intracellular permeability, compared to various polyethylene glycol (VPG), ST induced Cl- secretion was sluggish in onset and of shorter duration.

Studies were then carried out to determine the involved transport pathways. Secretion of bumetanide inhibited Cl- secretion in response to ST, but it had no effect on ion transport in the basal state, suggesting the involvement of the Na+ - K+ - 2Cl- co-transport system in Cl- secretion. The toxin had no effect on bumetanide sensitive 38Rb efflux, but increased the rate of bumetanide insensitive 38Rb efflux almost two fold. These observations suggest that ST does not directly affect the activity of the Na+ - K+ - 2Cl- co-transport system in Tg4 cells. The addition of barium chloride (K+ channel blocker) to the basolateral side did not inhibit the ST induced increase in Isc while mucosal addition had little or no effect. Similar to bumetanide, barium had no effect on the basal Isc or on unidirectional Na+ and Cl- fluxes. Ouabain, a Na+ - K+ - ATPase inhibitor, also inhibited and reversed ST induced Isc when added to the serosal reservoir. The existence of a K+ channel was suggested by the following observations: (a) the addition of ST increased 38Rb efflux into the serosal bath by 2-fold, while mucosal bath levels did not change; (b) Isc response of ST to barium inhibition was identical to that seen with barium inhibition of VIP or PGE2 mediated Isc, but quite different from carbachol induced Isc; (c) 38Rb efflux induced by the combination of ST and VIP was not different from the 38Rb efflux induced by VIP or ST alone; (d) bumetanide and ouabain had no effect, suggesting that this K+ channel operates independent of the Na+ - K+ - 2Cl- co-transport pathway and the Na+ - K+ - ATPase pump.

These results suggest the presence of two types of K+ channels which operate independently: Determination of cellular nucleotide levels showed that ST and not VIP or carbachol increased cGMP levels. These data suggest that the action of ST is mediated by cGMP alone and involves the Na+ - K+ - ATPase pump, Na+ - K+ - 2Cl- co-transport system, a Cl- exit channel and a K+ recycling channel, independent of each other.
Comment: ETIC produces two types of toxins, heat-labile (LT) and heat-stable (ST) (J Infect Dis 1980; 142: 278-84). In contrast to LT, ST does not activate adenylate cyclase and has no biochemical similarity to cholera toxin. ST is known to produce net intestinal fluid and electrolyte secretion through a second messenger, namely GMP (NatureL (London) 1981; 305: 70). But, how increased cellular GMP levels lead to the final effect of net fluid and electrolyte secretion is not clearly understood. Studies in cellular model systems have the advantage of being able to control all the cells alike. However, the cell may not have the same growth characteristics. So the study could be useful only if those cells are similar to in vivo cells both structurally and functionally. In this study, the authors studied the mechanism in a cell line (T47D) which resembles crypt cells morphologically (J Cell Biol 1983; 101: 2124-33). The T47D cell line is a secretory cell line, and this may allow better elucidation of the secretory mechanism. It has been shown that Cl- secretion across T47D cell monolayers results from a coordinated interaction of four transport pathways (J Clin Invest 1985; 75: 1855-65): (a) the Na+, K+-ATPase pump which provides the driving force, (b) a Na+, K+-Cl-co-transport system that serves as the Cl- uptake pathway, (c) a K+-channel which serves to recycle the K+, and (d) a Cl- channel that serves as the Cl- exit step. The first three pathways are located basolaterally while the Cl- exit channel is located apically. K+ and Cl- channels have been shown to be regulated directly and independently of the Na+, K+-Cl-co-transporter or the Na+, K+-ATPase pump. This mechanism has been well demonstrated for epithelial cells (ATPase and Ca++) but whether the same mechanism exists for GMP also has not been shown. In this study, the authors investigated the mechanism of action of ST and compared the results with Ca++ or GMP mediated secretory responses.

Cl- exit across the apical membrane occurs by the Cl- channel. The receptors for ST are also localized in the apical surface, as shown by receptor-binding assay studies (J Physiol 1985; 372: 189-200). This channel works along with the Na+, K+-ATPase pump which is localized at the basolateral membrane. The system helps in Cl- uptake across the basolateral membrane. The secretion of Cl- across the apical membrane is driven by Na+, K+-ATPase and its uptake across the basolateral membrane, thus producing a net Cl- secretion. Both the systems have to be functional for Cl- secretion to occur. The involvement of the Na+, K+-co-transport pathway was documented by the use of bumetanide. This drug is a loop diuretic and, as it blocks this pathway, the decrease in net Cl- secretion as observed in this study was expected. This observation was reported in an earlier study also (J Clin Invest 1983; 71: 462-71). The increased activity of this system requires an active Na++, K+-ATPase pump and is probably secondary to the favorable gradient created by Na+ and Cl- exit, the primary regulatory processes by ST. K+ exit occurs across the K+ channel localized on the basolateral membrane and the direct evidence for this is provided by the observation that it is subject to inhibition by barium. The K+ effect causes depolarization of the cell and then produces a driving force for Cl- exit across the apical membrane (Ann J Physiol 1985; 250: C486-94) and also prevents excessive intracellular accumulation of K+. This K+ transport pathway is also reported earlier for cAMP sensitive pathways, VIP and PGE (Ann J Physiol 1985; 250: C486-94), but differs from that of Ca++ mediated mechanisms reported for barium (J Clin Invest 1986; 77: 1211-21). This means that two different K+ channels exist, one for cAMP and cGMP and the other one for calcium. This observation is further supported by the results in the present study that K+ efflux induced by ST is not additive to that induced by VIP but is additive to that induced by cAMP. The increased Cl- secretion in response to ST differs from the cAMP mediated effect in two ways: (a) the time interval required to observe increased Cl- secretion with ST is longer perhaps because of the slower intracellular mechanism by which ST activates guanylate cyclase, and (b) the maximal effect of ST on Cl- secretion is less than that of VIP, which could be either because cGMP is less effective than cAMP in activating the protein kinase responsible for opening the Cl- channel, or because cAMP and cGMP open two different sets of Cl- channels. The finding that the combined effect of cGMP and cAMP (ST + VIP) approximated that induced by cAMP alone argues against the latter proposal.

In summary, ST of E coli causes secretion diarrhea through cAMP which mediates its effect via involvement of four transport pathways. Cellular cGMP exerts direct effects on the Cl- and K+ channels. The exit of these two ions activates the Na+, K+-ATPase on the basolateral membrane which in turn stimulates the Na+, K+-Cl-co-transport system, helping in Cl- uptake across the basolateral membrane. The Cl- exit, however, is much more than its uptake, which results in net Cl- secretion and secretory diarrhea. The authors have convincingly shown the mechanism of action of ST of E coli by these elegant studies. Not only are these observations of great pathophysiological interest, these have obvious therapeutic relevance. It would be logical now to investigate the therapeutic usefulness of various agents such as bumetanide, chloride channel blockers or ouabain in the treatment of ETIC diarrhea.

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INDEX TO ADVERTISERS

| Biological E Ltd | 134 |
| Bioessays Medicine Ltd | 189 |
| Bioessays Ltd | 163 |
| Biopro Ltd | 155 |
| D P Medical Diagnostics Pvt Ltd | 222 |
| D S Medical Diagnostics Pvt Ltd | 222 |
| D S Medical Diagnostics Pvt Ltd | 222 |
| Ekaled Ltd | 139, 169, 187, 175 |
| Glaxo Pharmaceuticals Ltd Ltd | 154 |
| Gufi Ltd | 185 |
| Heechein India Ltd | 210 |
| Indocon Remedies Ltd | 170 |
| Infral India Ltd | 174, 180, 220, 266 |
| J Hh Chemicals & Pharmaceuticals Ltd | 140 |
| J Mitra & Bros Pvt Ltd | 208 |
| J Mitra & Bros Pvt Ltd | 208 |
| Khandelwal Laboratories Ltd | 170 |
| Khandelwal Laboratories Ltd | 150 |

Lupin Laboratories Limited | 221 |
Mey & Baker (India) Ltd | 166 |
Merck Ltd | 140 |
Pfizer Ltd | 149, 160, 209 |
Rainbaxy Laboratories Ltd | 214 |
ROC Pharmaceuticals Ltd | 142 |
Ropakhos, Berti & Co. Ltd | 199-200 |
Searle (India) Ltd | 144 |
Serum Institute of India Ltd | 156 |
Sun Pharmaceuticals Industries | 190 |
Tata Pharmaceuticals Ltd | 170, Inside Back Cover |
Trent Pharmaceutical Pvt Ltd | 136, Inside Front Cover |
U S Vitamin (India) Ltd | 141 |
Wallace Pharmaceuticals Ltd | 147 |
Vitamin - Hindustan | 194 |
Yash Pharmaceuticals Ltd Pvt Ltd | 197 |

ININDIAN J GASTROENTEROL Vol 8 No 3 JUly 1989

SELECTED SUMMARIES 219