Progress report

Small bowel resection and gastric acid hypersecretion

Resection of a large segment of small intestine in the dog is associated with an increase in gastric acid secretion[1-18]. However, the occurrence of gastric acid hypersecretion after small bowel resection in man remains in doubt. The benign postoperative course of patients who have undergone an extensive intestinal resection after having had a previous gastric resection was first observed by Craig and Stewart (1960)[19]. Since then, the beneficial effect on survival of measures to control gastric acid secretion after extensive small bowel resection has been well documented[4,20].

An acute syndrome consisting of the aspiration of copious quantities of acid from the stomach after small bowel resection has been reported in man[14,21]. The copious aspirate usually subsides in the first few weeks after surgery. There are few reports of long-term changes in acid secretion after small bowel resection or exclusion. A low pH of the jejunal contents in six patients of Krone, Theodore, Sleisinger, and Jeffries[22] suggests that hypersecretion exists after small bowel resection. However, the work of Shibata, McKenzie, and Long[23], Salmon and Wright[24], and Buchwald and Varco[25] has not confirmed the increase in acid secretion in patients undergoing small bowel bypass. In man, therefore, the circumstantial evidence that is available suggests that there is a syndrome of hypersecretion after small bowel resection but the few studies of acid secretion which have been reported have not verified the presence of this syndrome.

Although 50 years have elapsed since gastric acid hypersecretion after extensive small bowel resection was first demonstrated experimentally[1], knowledge of the mechanisms by which hypersecretion occurs is still fragmentary. The increase in gastric secretion has been found to be proportional to the length of the intestine resected[5,7]. Controversy exists over which segment of the intestine, when removed, produces the greater increase in gastric acid secretion. A greater increase in gastric acid secretion was found after resection of the upper small intestine compared with the lower small intestine[2,4,11,12], whereas other authors have demonstrated a greater increase in gastric acid secretion after resection of the lower small intestine[6,7].

The acid response to exogenous stimulation of the parietal area either by histamine or gastrin is essentially unaffected by small bowel resection[6,11,25], suggesting that the increase in acid secretion is confined to the acid response from a meal and is not related to a change in parietal cell function. The marked prolongation of the acid response to a meal after intestinal resection provides additional evidence that it is the later part of the meal response which is abnormal[14]. A similar observation has been made by other authors, who reported difficulty in achieving a basal secretory state in dogs which had undergone an extensive intestinal resection[5,11,9].

In dogs with an antrectomy and a vagally denervated gastric pouch, an

increase in acid secretion of the same relative magnitude has been found after small bowel resection as in dogs with an intact gastric antrum[8,15]. These studies suggest that the gastric antrum is not essential for the production of gastric hypersecretion, and that it is the remaining stimulus to gastric acid secretion, namely the small intestine itself, that is important in the production of the increase in acid secretion.

An increase in gastric acid secretion was observed after a reversal of short segments of the small intestine, whether alone or in combination with small bowel resection[26,27], thus suggesting that stasis of food in the antrum or in the intestine is of importance in the production of hypersecretion which follows the reversal of an intestinal loop. Although gastric acid hypersecretion was found to follow intestinal resection or reversal in these experiments it is possible that the hypersecretion could be the result of two different mechanisms.

A recent series of experiments in the dog into the relationship between extensive small bowel resection and gastric hypersecretion confirmed that there was a prolongation of the acid response to a meal after intestinal resection[28]. Further, an abnormal stimulatory mechanism occurred when food passed into the remaining segment of the small intestine and stimulation from the antrum and vagus was essentially unchanged after intestinal resection[29]. In another series of experiments, using dogs with a duodenal fistula, macroscopic faecal contamination of the duodenal contents was found in all dogs which were demonstrating gastric acid hypersecretion after small bowel resection[30]. In addition, there was a delay in transit of food through the remaining segment of the small bowel. These experiments also cast doubt about the importance of loss of intestinal inhibition in producing hypersecretion[31]. In a parallel series of experiments, the magnitude of the intestinal phase of gastric acid stimulation was re-appraised and found to be of greater magnitude than previously recognized[32], and after resection of the small intestine, stimulation from the remaining small bowel was even greater[29].

It is interesting to speculate how such an increase in stimulation after an extensive small bowel resection might occur when food is present in the remaining segment of the small intestine. Statis of food in the upper small intestine could result in the increased breakdown of protein in the upper small bowel. Peptide fragments and amino acids in contact with the mucosa of the small bowel are known to produce secretion of acid from the stomach in the same way that these substances produce stimulation of acid when in contact with the antral mucosa. Gastrin-like substances have been isolated from the mucosa of the upper small intestine in both man and dog[33-40]. The amount of intestinal gastrin is greatest in the duodenum and decreases down the length of the small intestine[36]. Increased breakdown of food substances in the duodenum and proximal small bowel after intestinal resection as a result of intestinal stasis could result in a greater stimulation of acid through the greater release of an intestinal humoral stimulant.

Abnormal contamination of the upper small bowel after extensive intestinal resection has been confirmed in both man and the dog[22]. In our experience, the gastric acid hypersecretion was periodic in nature and corresponded to changes in the bacterial flora of the upper small intestine[30]. Normally, the upper small bowel contains relatively few bacteria, consisting of predominantly Gram-positive aerobes of the oral type with a total concentration of

less than 10^5 organisms per ml, whereas the terminal ileum has a substantially greater number of bacteria, between 10^5 and 10^8 organisms per ml, comprising a mixture of Gram-positive and Gram-negative organisms bearing a greater resemblance to caecal flora than does the flora of the jejunum[41–50].

The presence of bacteria in the intestine can affect the intestinal wall. The intestinal wall of a germ-free or antibiotic-treated animal is thinner and lighter in weight than that of appropriate controls[51,52,53]. When the enteric flora is reduced or eliminated, marked reduction is noted in the numbers of leucocytes, plasma cells, lymphocytes, histiocytes, and macrophages present in the lamina propria[51,52,54,55,56]. Increased numbers of lymphocytes and reticulocytes appear in the lamina propria when the germ-free animal is contaminated with *Cl welchii*[51,54] or *Strep faecalis*[51]. These changes in the lamina propria have been called 'physiological inflammation'[54]. Sprinz[54] has also associated changes in the intestinal villous architecture with the presence of enteric bacteria. The villi of germ-free animals are slender and regular in comparison with the thicker, shorter, and irregular processes of conventionally reared animals. Release of a stimulatory substance, possibly gastrin, from the mucosa of the duodenum and upper jejunum by the action of colonic bacteria (or their products), which are not normally present in the upper small intestine, is another possible mode of stimulation from the upper small bowel.

Release of a humoral stimulant from the intestinal mucosa might be caused also by the presence of 'toxic' products from microbial action on dietary foodstuffs. Such products include hydroxystearic acids which are similar to ricinoleic acid, the main constituent of castor oil [57–61], acetic, lactic, and formic acids[62]. Normally, bacterial degradation of food substances occurs in the lower small bowel and colon, where bacterial populations are greatest; intestinal stasis and bacterial overgrowth in the duodenum and upper jejunum after small bowel resection might produce these 'toxic' substances at a more proximal level in the intestine.

The action of bacteria on the bile acids in the upper jejunum and duodenum suggests yet another possible mode of release of a humoral stimulant from the upper small bowel mucosa. Recent studies have shown that a wide range of intestinal bacteria, particularly Gram-negative anaerobic organisms, can deconjugate and transform bile acids by dehydroxylation, oxidation, and reduction[63–83]. Other studies have shown that intestinal bacteria increase turnover and the metabolic rate of cholic acid in germ-free animals[84,85]. Free bile acids are abnormal in the upper small intestine[86–90] although they are present in the terminal ileum, from where both conjugated and unconjugated bile acids are normally absorbed into the portal circulation[91–100,89,81,101,102,90]. Increased concentrations of deconjugated or free bile acids have been found in the upper gastrointestinal tract, in association with abnormal bacterial flora, in patients after an extensive small bowel resection[22].

Free bile acids and their derivatives have a high degree of lytic activity on the walls of certain bacteria[103]. These substances also produce inflammation when injected intramuscularly; lithocholic acid and its derivatives are particularly potent[104]. A similar toxic effect was observed when bile acid derivatives were placed in contact with the duodenal and jejunal mucosa in sufficient concentration[87,70]. However, this effect is not demonstrable by light microscopy if physiological concentrations of bile acid derivatives are

used[69,70,74]. More recently, changes have been demonstrated by electron microscopy in the mucosa of a blind small bowel loop in rats[105,106]. These changes are similar to those caused by feeding small amounts of deconjugated bile salts to normal rats[107].

Inflammation of the lamina propria or contact of the mucosa with potentially toxic bile acid derivatives could release a stimulatory substance which acts on the parietal cell area in a way similar to that in which normal conjugated bile acids can release gastrin from the antrum[108]. Support for the belief that bile acids normally play an intermediary role in stimulation of acid secretion arising from food in the small bowel is provided by the experiments of Nahrwold and Grossman[109] which showed a decrease in the acid response to a meal after temporarily diverting the bile from the intestine. They postulated that the presence of bile salts in the intestine facilitates the intestinal phase of gastric secretion. Their findings are at variance with those of Menguy[110,111,112], Menguy and Mings[113], and Landor, Behringer, and Wild[16] who found an increase in acid secretion after chronic biliary diversion. Unlike the experiments of Nahrwold and Grossman[109], Menguy[110] found that restoration of the normal bile flow was not associated with a return of gastric secretion to normal. Also, in dogs with chronic biliary diversion, liver function studies were abnormal, suggesting that liver dysfunction might account for some of the changes in acid secretion. An alternative explanation for the different result of Menguy[110,111,112] might be that bacterial overgrowth occurs in the intestine as the result of interference with the normal controlling influence of bile in the intestine, which, in turn, might produce increased acid stimulation[114].

Abnormal stimulation from food in the upper small intestine could account for the prolongation of the acid response to a meal and difficulty in achieving a basal secretory state after intestinal resection, and also for the prolonged response to a meal after truncal vagotomy[115]. The wide fluctuations in the 24-hour acid secretions after intestinal resection[28] might be explained also by changes in the bacterial flora in the upper small bowel.

Many small bowel disorders which are associated with steatorrhoea have been found to have associated gastric hypersecretion. For example, steatorrhoea and acid hypersecretion have been observed after small bowel resection[22,2], reversed intestinal loops[26,27], blind loops of the Mann and Williamson type[116], and after truncal or extragastric vagotomy[117,13].

Bacterial overgrowth in the upper small intestine is found frequently in conditions associated with steatorrhoea[118,87,69]. Similarly, bacterial overgrowth has been found in conditions associated with gastric acid hypersecretion, small bowel resection[22,119], and truncal or extragastric vagotomy[120-123].

Steatorrhoea due to bacterial overgrowth in the small intestine is generally attributed to the effect of deconjugated or degraded bile salts[87,69,70,72,75]. However, altered bile salt metabolism alone does not entirely explain the steatorrhoea in patients with small bowel bacterial overgrowth. Complete biliary obstruction or diversion often produces only modest faecal fat losses, whereas steatorrhoea in the blind loop syndrome may be severe[123]. These observations suggest that bacteria in the upper intestine exert harmful effects other than by disturbance of bile salt metabolism. Coincidental gastric hypersecretion in the bacterial overgrowth syndrome might account for the severe steatorrhoea observed occasionally in these conditions. A

relatively acid pH in the jejunum impairs micelle formation and lipolysis and also reduces the solubility of fatty acids in bile micelles[124,22]. In addition, carbohydrate metabolism is inefficient in the presence of an acid pH[125].

Figure 1 is a diagrammatic representation of the possible interrelationships between some small bowel disorders, gastric hypersecretion, and steatorrhoea. Abnormal release of an intestinal stimulatory substance as the result of bacterial overgrowth could account not only for most of the observations made in our experiments[28-32] but also for many hitherto unexplained findings.

The increased acid response to a meal after reversal of a small bowel loop was attributed to antral stasis and greater release of antral gastrin[26,27]. An alternative hypothesis is that excessive stimulation from food in the upper small bowel is the result of intestinal stasis. It would be interesting to test this hypothesis by seeing if hypersecretion occurred after reversing a small intestinal loop in antrectomized dogs.

The increase in acid secretion after truncal vagotomy or extragastric vagotomy in dogs with Heidenhain pouches cannot be explained satisfactorily on the basis of the knowledge that is currently available[126-130]. This led Emas and Grossman[131], Stening and Grossman[132], Spencer and Grossman[133], and Korman, Hansky, and Scott[134] to postulate that the vagus normally exerts a controlling influence on a stimulatory substance, outside the stomach, which is released in greater quantities after section of the extragastric branches of the vagi. The increased acid secretion after extragastric vagotomy could also be explained on the basis of an abnormal
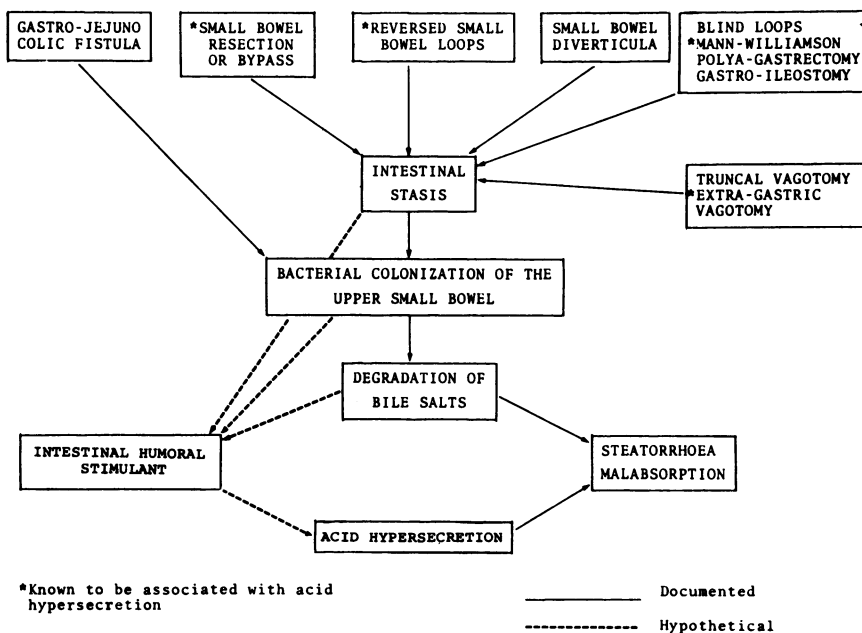

Fig 1 *Hypothesis showing the possible interrelationship of various small bowel disorders, gastric acid hypersecretion, and steatorrhoea.*

excitatory process in the upper intestine, occurring as a result of a motility disturbance created by vagotomy.

The acid hypersecretion and the peptic ulcer diathesis which occurs in dogs which have the duodenal loop transplanted into the terminal ileum (the Mann-Williamson preparation)[135,116] have not been explained satisfactorily. Loss of the neutralizing effect of alkaline duodenal secretions from the region of the gastro-jejunostomy does not seem important because McCann[136], Ivy, and Fauley[137] and Maier and Grossman[138] found that ulceration still occurred when the duodenal secretions were returned to the stomach. Furthermore, a different explanation is required to account for the actual increase in gastric acid secretion which occurs in this syndrome[139].

The proximity of the blind duodenal loop to the ileo-caecal valve was pointed out by Mann and Williamson in their original paper[116]. Transplantation of the duodenal loop to the middle and upper small intestine was found to be associated with lesser degrees of ulcer formation[140,141], and, so far, this difference has not been adequately explained.

The gastric antrum is not necessary for the occurrence of hypersecretion in the Mann-Williamson model[142], implying that the abnormal mechanism does not necessarily involve antral gastrin.

Interference with the fat inhibitory mechanism as a cause of the hypersecretion found in the Mann-Williamson preparation was proposed by Menguy and Mings[113]. They provided evidence that gastric hypersecretion could result from diversion of bile or pancreatic juice alone to the lower small bowel, but they could not explain the acid changes without involving the gastric antrum. This led Menguy[111,112] to examine the effect of pancreatic and biliary diversion on liver function. Although abnormalities in liver function were found, their relevance to acid hypersecretion was unknown.

Evidence that there is loss of duodenal inhibition elicited by acid following transplantation of the duodenum to the terminal ileum was produced by the study of Manzano, de la Rosa, Woodward, and Dragstedt[143]. However, like Menguy and Mings[113], they concluded that the importance of this mechanism is in doubt because it is thought to act through inhibition of antral gastrin and the presence of the antrum has been found to be unnecessary[142]. Manzano, de la Rosa, Woodward, and Dragstedt[143], therefore, postulated that there was a true increase in acid secretion as well as interference with inhibition to account for the hypersecretion.

The profound increase in acid secretion in the Mann-Williamson preparation can be explained readily by the current hypothesis. Colonization of the blind duodenal loop occurs because of the proximity to the colon. The presence of colonic bacteria alone or the effect of these bacteria on food substances or bile salts in the upper small bowel could release a stimulatory hormone from the mucosa of the duodenum.

Intestinal stasis and overgrowth of bacteria, leading to increased stimulation when food is present in the upper small bowel, might provide a common explanation for the increased gastric acid secretion which follows small bowel resection or exclusion, reversal of intestinal loops, extragastric vagotomy, or the construction of a blind loop, such as in the Mann-Williamson preparation.

It will be interesting to await the results of gastrin estimations in patients with small bowel resection, exclusion, reversal, or in patients with a blind intestinal loop, to see if the proposed extragastric or intestinal humoral

stimulant is in fact gastrin as would appear to be the case in patients who have undergone truncal vagotomy[134].

BRIAN BUXTON

Department of Surgery,
Royal Melbourne Hospital, Victoria,
Australia

References

[1]Stassoff, B. (1914). Experimentelle Untersuchungen über die Kompensatorischen Vorgänge bei Darmresektion. *Beitr. Klin. Chir.*, 89, 527-586.
[2]Sabsai, B. I. (1963). The effect of extensive resection of the proximal and distal portions of the small intestine on canine gastric secretion. *Bull. exp. Biol. Med.*, 55, 387-390. Also *Byull. éksp. Biol. Med.*, 55 (4), 32-36 (Russian).
[3]Landor, J. H., and Baker, W. K. (1964). Gastric hypersecretion produced by massive small bowel resection in dogs. *J. surg. Res.*, 4, 518-522.
[4]Westerheide, R. L., Elliot, D. W., and Hardacre, J. M. (1965). The potential of the upper small bowel in regulating acid secretion. *Surgery*, 58, 73-81.
[5]Frederick, P. L., Sizer, J. S., and Osborne, M. P. (1965). Relation of massive bowel resection to gastric secretion. *New Engl. J. Med.*, 272, 509-514.
[6]Reul, G. J., and Ellison, E. H. (1966). Effect of seventy-five per cent distal small bowel resection on gastric secretion. *Amer. J. Surg.*, III, 772-776.
[7]Osborne, M. P., Frederick, P. L., Sizer, J. S., Blair, D., Cole, P., and Thum, W. (1966). Mechanism of gastric hypersecretion following massive intestinal resection: clinical and experimental observations. *Ann. Surg.*, 164, 622-634.
[8]Kerr, G., Elliot, D. W., and Endahl, G. L. (1968). Effect of antrectomy on gastric acid hypersecretion induced by isolation of the proximal small bowel. *Amer. J. Surg.*, 115, 157-164.
[9]Yakimets, W. W., and Bondar, G. F. (1969). Hormonal stimulatory mechanism producing gastric hypersecretion following massive small intestinal resection. *Canad. J. Surg.*, 12, 241-244.
[10]Windsor, C. W. O. (1968). Gastric secretion following massive small intestinal resection. *Brit. J. Surg.*, 55, 392.
[11]Copeland, E. M., Miller, L. D., and Smith, G. P. (1968). The complex nature of small bowel control of gastic secretion. *Ann. Surg.*, 168, 36-46.
[12]Santillana, M., Wise, L., Schuck, M., and Ballinger, W. F. (1969). Changes in gastric acid secretion following resection or exclusion of different segments of the small intestine. *Surgery*, 65, 777-782.
[13]Burrington, J. D., and Hamilton, J. R. (1969). Steatorrhea after massive bowel resection: effects of surgical reduction of gastric acid secretion. *Surg. Forum*, 20, 341-343.
[14]Windsor, C. W. O., Fejfar, J., and Woodward, D. A. K. (1969). Gastric secretion after massive small bowel resection. *Gut*, 10, 779-786.
[15]Landor, J. H. (1969). Intestinal resection and gastric secretion in dogs with antrectomy. *Arch. Surg.*, 98, 645-646.
[16]Landor, J. H., Behringer, B. R., and Wild, R. A. (1970). The effect of enterectomy on gastric secretion in dogs with biliary fistulas. *Amer. J. dig. Dis.*, 15, 633-636.
[17]Landor, J. H., Behringer, B. R., and Wild, R. A. (1971). Postenterectomy gastric hypersecretion in dogs: the relative importance of proximal versus distal resection. *J. surg. Res.*, 11, 238-242.
[18]Saik, R. P., Copeland, E. M., Miller, L. D., and Smith, G. P. (1971). Effect of ileal exclusion on the Heidenhain pouch acid response to histamine in dogs. *Ann. Surg.*, 173, 67-77.
[19]Craig, T. V., and Stewart, W. R. C. (1960). Massive bowel resection in a patient with 75 per cent gastrectomy. *Surgery*, 48, 678-681.
[20]Osborne, M. P., Sizer, J., Frederick, P. L., and Zamcheck, N. (1967). Massive bowel resection and gastric hypersecretion: its mechanism and a plan for clinical study and management. *Amer. J. Surg.*, 114, 393-397.
[21]Aber, G. M., Ashton, F., Carmalt, M. H. B., and Whitehead, T. P. (1967). Gastric hypersecretion following massive small-bowel resection in man. *Amer. J. dig. Dis.*, 12, 785-794.
[22]Krone, C. L., Theodor, E., Sleisenger, M. H., and Jeffries, G. H., (1968). Studies on the pathogenesis of malabsorption. Lipid hydrolysis and micelle formation in the intestinal lumen. *Medicine (Baltimore)*, 47, 89-106.
[23]Shibata, H. R., MacKenzie, J. R., and Long, R. C. (1967). Metabolic effects of controlled jejunocolic bypass. *Arch. Surg.*, 95, 413-428.
[24]Salmon, P. A., and Wright, W. J. (1968). Effect of small-bowel bypass on gastric secretion in obese patients. *Canad. J. Surg.*, 11, 365-368.
[25]Buchwald, H., and Varco, R. L. (1970). Human gastric secretory studies following distal small bowel bypass. *Gastroenterology*, 58, 931.
[26]Grundberg, A. B., Lopez, A. S., and Dragstedt, L. R., II. (1967). Effect of intestinal reversal and massive resection on gastric secretion. *Arch. Surg.*, 94, 326-329.
[27]Kimura, S., and Dragstedt, L. R. II. (1969). Reversed jejunal segments and gastric hypersecretion. *Arch. Surg.*, 98, 713-715.
[28]Buxton, B., Wasunna, A. E. O., Saunders, J., and Gillespie, I. E. (1972). Gastric acid secretion after small bowel resection on exclusion in dogs: comparison of vagally innervated and denervated gastric pouches. *R.C. rom. Gastro-ent.*, 4, 81-86.
[29]Buxton, B., Wasunna, A. E. O., Saunders, J., and Gillespie, I. E. (1972). Site of the abnormal stimulus of gastric secretion after small bowel exclusion. *Gut*, 13, 539-543.
[30]Buxton, B., Saunders, J., and Wasunna, A. E. O. (1973). The effect of truncal vagotomy and pyloroplasty on the increase in gastric acid secretion following small-bowel resection. *Aust. N.Z. J. Surg.*, 42, 318.
[31]Buxton, B. (1973). Effect of small bowel resection on gastric acid secretion. M.S. Thesis, University of Melbourne.

[32]Buxton, B., Wasunna, A. E. O., Bedi, B. S., and Gillespie, I. E. (1972). Role of the jejunum and the ileum in the acid response of dogs to a meal. *Gastroenterology*, 63, 270-272.

[33]Komarov, S. A. (1938). Gastrin. *Proc. Soc. exp. Biol.* (*N.Y.*), 38, 514-516.

[34]Harper, A. A. (1946). The effect of extracts of gastric and intestinal mucosa on the secretion of HCl by the cat's stomach. *J. Physiol.* (*Lond.*), 31P.

[35]Uvnäs, B. (1945). The presence of a gastric secretory excitant in the human gastric and duodenal mucosa. *Acta physiol. scand.*, 10, 97-101.

[36]Lai, K. S. (1964). Part II quantitative study of the distribution of gastrin-like activity along the gut. *Gut*, 5, 334-341.

[37]Gregory, R. A. (1968). The intestinal phase. In *The Physiology of Gastric Secretion*, edited by L. S. Semb and J. Myren, pp. 257-263. Universite's Forlaget, Oslo.

[38]Emås, S., and Fyrö, B. (1968). Gastrin-like activity in different parts of the gastrointestinal tract of the cat. *Acta physiol. scand.*, 74, 359-367.

[39]Emås, S., Borg, I., and Fyrö, B. (1971). Antral and duodenal gastrin activity in non-ulcer and ulcer patients. *Scand. J. Gastroent.*, 6, 39-43.

[40]Berson, S. A., and Yalow, R. S. (1971). Nature of immunoreactive gastrin extracted from tissues of the gastrointestinal tract. *Gastroenterology*, 60, 215-222.

[41]Cregan, J., and Hayward, N. J. (1953). The bacterial content of the healthy human small intestine. *Brit. med. J.*, 1, 1356-1359.

[42]Cregan, J., Dunlop, E. E., and Hayward, N. J. (1953). The bacterial content of human small intestine in disease of stomach. *Brit. med. J.*, 2, 1248-1251.

[43]Martini, G. A., Phear, E. A., Ruebner, B., and Sherlock, S. (1957). The bacterial content of the small intestine in normal and cirrhotic subjects: relation to methionine toxicity. *Clin. Sci.*, 16, 35-51.

[44]Goldstein, F., Wirts, C. W., and Josephs, L. (1962). The bacterial flora of the small intestine. *Gastroenterology*, 42, 755-756.

[45]Shiner, M., Waters, T. E., and Gray, J. D. A. (1963). Culture studies of the gastrointestinal tract with a newly devised capsule: results of tests *in vitro* and *in vivo*. *Gastroenterology*, 45, 625-632.

[46]Donaldson, R. M., Jr. (1964). Normal bacterial populations of the intestine and their relation to intestinal function. *New Engl. J. Med.*, 270, 938-946, 1050-1056.

[47]Kalser, M. H., Cohen, R., Arteaga, I., Yawn, E., Mayoral, L., Hoffert, W. R., and Frazier, D. Normal viral and bacterial flora of the human small and large intestine. *New Engl. J. Med.*, 274, 500-505, 558-563.

[48]Gorbach, S. L., Plaut, A. G., Nahas, L., Weinstein, L., Spanknebel, G., and Levitan, R. (1967). Studies of intestinal microflora. II. Microorganisms of the small intestine and their relation to oral and fecal flora. *Gastroenterology*, 53, 856-867.

[49]Drasar, B. S., Shiner, M., and McLeod, G. M. (1969). Studies on the intestinal flora. I. The bacterial flora of the gastrointestinal tract in healthy and achlorhydric persons. *Gastroenterology*, 56, 71-79.

[50]Gorbach, S. L. (1971). Intestinal microflora. *Gastroenterology*, 60, 1110-1129.

[51]Gordon, H. A. (1960). The germ-free animal: its use in the study of 'physiologic' effects of the normal microbial flora on the animal host. *Amer. J. dig. Dis.*, 5, 841-867.

[52]Coates, M. E., Davies, M. K., and Kon, S. K. (1955). The effect of antibiotics on the intestine of the chick. *Brit. J. Nutr.*, 9, 110-119.

[53]Draper, H. H. (1958). The absorption of radiolysine by the chick as affected by penicillin administration. *J. Nutr.*, 64, 33-42.

[54]Sprinz, H. (1962). Morphological response of intestinal mucosa to enteric bacteria and its implication for sprue and Asiatic cholera. *Fed. Proc.*, 21, 57-64.

[55]Gordon, H. A., and Bruckner-Kardoss, E. (1961). Effect of normal microbial flora on intestinal surface area. *Amer. J. Physiol.*, 201, 175-178.

[56]Abrams, G. D., Bauer, H., and Sprinz, H. (1963). Influence of the normal flora on mucosal morphology and cellular renewal in the ileum: a comparison of germ-free and conventional mice. *Lab. Invest.*, 12, 355-364.

[57]Thomas, P. J. (1960). In vitro conversion of oeleic acid to hydroxy stearic acid by intestinal bacteria. *Clin. Res.*, 18, 609.

[58]Webb, J. P. W., James, A. T., and Kellock, T. D. (1963). The influence of diet on the quality of faecal fat in patients with and without steatorrhoea. *Gut*, 4, 37-41.

[59]Frazer, A. C. (1961). Role of lipids in normal metabolism. *Fed. Proc.*, 20, Suppl. 7, 146-151.

[60]Kim, Y. S., and Spritz, N. (1968). Metabolism of hydroxy fatty acids in dogs with steatorrhoea secondary to experimentally produced intestinal blind loops. *J. Lipid Res.*, 9, 487-491.

[61]Larson, N. L., and Hill, E. G. (1960). Amine formation and metabolic activity of microorganisms in the ileum of young swine fed chlortetracycline. *J. Bact.*, 80, 188-192.

[62]Weijers, H. A., Kamer, J. H., van de Dicke, W. K., and Ijsseling, J. (1961). Diarrhoea caused by deficiency of sugar splitting enzymes. *Acta paediat.* (*Uppsala*), 50, 55-71.

[63]Norman, A., and Grubb, R. (1955). Hydrolysis of conjugated bile acids by clostridia and enterococci. *Acta path. microbiol. scand.*, 36, 537-547.

[64]Lindstedt, S., and Norman, A. (1956). The excretion of bile acids in rats treated with chemotherapeutics: bile acids and steroids 40. *Acta physiol. scand.*, 38, 129-134.

[65]Lindstedt, S., and Norman, A. (1956). The turnover of bile acids in the rat: bile acids and steroids 39. *Acta physiol. scand.*, 38, 121-128.

[66]Lindstedt, S., and Sjövall, J. (1957). On the formation of deoxycholic acid from cholic acid in the rabbit. *Acta chem. scand.*, 11, 421-426.

[67]Norman, A., and Bergman, S. (1960). The action of intestinal micro-organisms on bile acids: bile acids and steroids 101. *Acta chem. scand.*, 14, 1781-1789.

[68]Norman, A., and Shorb, M. S. (1962). In vitro formation of deoxycholic and lithocholic acid by human intestinal micro-organisms. *Proc. Soc. exp. Biol.* (*N.Y.*), 110, 552-555.

[69]Donaldson, R. M., Jr. (1965). Studies on the pathogenesis of steatorrhea in the blind loop syndrome. *J. clin. Invest.*, 44, 1815-1825.

[70]Tabaqchali, S., and Booth, C. C. (1966). Jejunal bacteriology and bile-salt metabolism in patients with intestinal malabsorption. *Lancet*, 2, 12-15.

[71]Drasar, B. S., Hill, M. J., and Shiner, M. (1966). The deconjugation of bile salts by human intestinal bacteria. *Lancet*, 1, 1237-1238.

[72]Kim, Y. S., Spritz, N., Blum, M., Terz, J., and Sherlock, P. (1966). The role of altered bile acid metabolism in the steatorrhoea of experimental blind loop. *J. clin. Invest.*, 45, 956-962.

[73]Midtvedt, T. (1967). Properties of anaerobic gram positive rods capable of 7 α-dehydroxylating bile acids. *Acta path. microbiol. scand.*, 71, 147-160.

[74]Rosenberg, I. H., Hardison, W. G., and Bull, D. M. (1967). Abnormal bile-salt patterns and intestinal bacterial overgrowth associated with malabsorption. *New Engl. J. Med.*, 276, 1391-1397.

[75]Tabaqchali, S., Hatzioannou, J., and Booth, C. C. (1968). Bile-salt deconjugation and steatorrhoea in patients with the stagnant loop syndrome. *Lancet*, 2, 12-16.

[76]Midtvedt, T., and Norman, A. (1967). Bile acid transformations by microbial strains belonging to genera found in intestinal contents. *Acta path. microbiol. scand.*, 71, 629-638.

[77]Midtvedt, T., and Norman, A. (1968). Anaerobic, bile acid transforming microorganisms in rat intestinal content. *Acta path. microbiol. scand.*, 72, 337-344.

[78]Hill, M. J., and Drasar, B. S. (1968). Degradation of bile salts by human intestinal bacteria. *Gut*, 9, 22-27

[79]Shimada, K., Bricknell, K. S., and Finegold, S. M. (1969). Deconjugation of bile acids by intestinal bacteria: review of literature and additional studies. *J. infect. Dis.*, 119, 273-281.

[80]Aries, V., Crowther, J. S., Drasar, B. S., and Hill, M. J. (1969). Degradation of bile salts by human intestinal bacteria. *Gut*, 10, 575-576.

[81]Garbutt, J. T., Wilkins, R. M., Lack, L., and Tyor, M. P. (1970). Bacteria modification of taurocholate during enterohepatic recirculation in normal man and patients with small intestinal disease. *Gastroenterology*, 59, 553-566.

[82]Aris V. C., and Hill, M. J. (1970), The formation of unsaturated bile acids by intestinal bacteria. *Biochem. J.*, 119, 37-38.

[83]Floch, M. H. W., Gershengoren, W., Elliot, S., and Spiro, H. M. (1971). Bile acid inhibition of the intestinal microflora—a function for simple bile acids? *Gastroenterology*, 61, 228-233.

[84]Gustafsson, B. E., Bergström, S., Lindstedt, S., and Norman, A. (1957). Turnover and nature of fecal bile acids in germ free and infected rats fed cholic acid—24-14C: bile acids and steroids 41. *Proc. Soc. exp. Biol. (N.Y.)*, 94, 467-471.

[85]Gustafsson, B. E., Norman, A., and Sjövall, J. (1960). Influence of E. coli infection on turnover and metabolism of cholic acid in germ-free rats. *Arch. Biochem.*, 91, 93-100.

[86]Haselwood, G. A. D. (1955). Recent developments in our knowledge of bile salts. *Physiol. Rev.*, 35, 178-196.

[87]Dawson, A. M., Isselbacher, K. J., and Bell, V. M. (1960). Studies on lipid metabolism in the small intestine with observations on the role of bile salts. *J. clin. Invest.*, 39, 730-740.

[88]Sjövall, J. (1960). Bile acids in man under normal and pathological conditions: bile acids and steroids. *Clin. chim. Acta*, 5, 33-41.

[89]Northfield, T. C., Condillac, E., and McColl, I. (1970). Bile salt metabolism in the normal human small intestine. *Gut*, 11, 1063.

[90]Northfield, T. C., and Condillac, E. (1971). Small intestinal bile salt metabolism in normal subjects and in the stagnant loop syndrome. *Clin. Sci.*, 40, 2P-2P.

[91]Lack, L., and Weiner, I. M. (1961). In vitro absorption of bile salts by small intestine of rats and guinea pigs. *Amer. J. Physiol.*, 200, 313-317.

[92]Bergström, S. (1962). Metabolism of bile acids, *Fed. Proc.*, 21, Suppl. 11, 28-32.

[93]Weiner, I. M., and Lack, L. (1962). Absorption of bile salts from the small intestine *in vivo. Amer. J. Physiol.*, 202, 155-157.

[94]Borgström, B., Lundh, G., and Hofmann, A. (1963). The site of absorption of conjugated bile salts in man. *Gastroenterology*, 45, 229-238.

[95]Glasser, J. E., Weiner, I. M., and Lack, L. (1965). Comparative physiology of intestinal taurocholate transport. *Amer. J. Physiol.*, 208, 359-362.

[96]Playoust, M. R., Lack L., and Weiner, I. M. (1965). Effect of intestinal resection on bile salt absorption in dogs. *Amer. J. Physiol.*, 208, 363-369.

[97]Holt, P. R. (1966). Competitive inhibition of intestinal bile salt absorption in the rat. *Amer. J. Physiol.*, 210, 635-639.

[98]Dietschy, J. M., Salomon, H. S., and Siperstein, M. D. (1966). Bile acid metabolism. I. Studies on the mechanisms of intestinal transport. *J. clin. Invest.*, 45, 832-846.

[99]Austad, W. I., Lack, L., and Tyor, M. P. (1967). Importance of bile acids and of an intact distal small intestine for fat absorption. *Gastroenterology*, 52, 638-646.

[100]Dietschy, J. M. (1968). Mechanisms for the intestinal absorption of bile acids. *J. lipid Res.*, 9, 297-309.

[101]Mallory, A., Smith, J., Kern, F., and Savage, D. (1971). Patterns of bile acids and microflora in the human small intestine. (Abstr.) *J. Lab. clin. Med.*, 78, 829-830.

[102]Tyor, M. P., Garbutt, J. T., and Lack, L. (1971). Metabolism and transport of bile salts in the intestine. *Amer. J. Med.*, 51, 614-626.

[103]Kozlowski, A. (1925). Comparative studies of the action on the pneumococcus of bile acids and unsaturated fatty acids found in bile in the form of soaps. *J. exp. Med.*, 42, 453-463.

[104]Palmer, R. H., Glickman, P. B., and Kappas, A. (1962). Pyrogenic and inflammatory properties of certain bile acids in man. *J. clin. Invest.*, 41, 1573-1577.

[105]Paulley, J. W. (1969). The jejunal mucosa in malabsorptive states with high bacterial counts. In *Malabsorption* (Pfizer Medical Monographs, No. 4) edited by R. H. Girdwood and A. N. Smith, pp. 171-176. University of Edinburgh Press, Edinburgh.

[106]Gracey, M. (1971). Intestinal absorption in the 'contaminated small bowel syndrome'. *Gut*, 12, 403-410.

[107]Shiner, M. (1969). The effect of bile acids on the small intestinal mucosa in man and rats: a light and electron microscopy study. In *Bile Acid Metabolism*, edited by L. Shiff, J. Carey, and J. D. Dietschy. Thomas, Springfield, Illinois.

[108]Bedi, B. S., Debas, H. T., Gillespie, G., and Gillespie, I. E. (1971). Effect of bile salts on antral gastrin release. *Gastroenterology*, 60, 256-262.

[109]Nahrwold, D. L., and Grossman, M. I. (1967). Effect of exclusion of bile from the intestine on gastric acid secretion. *Gastroenterology*, 52, 667-669.

[110]Menguy, R. (1961). Effect of biliary diversion from the small intestine on gastric secretory activity in dogs. *Gastroenterology*, 41, 568-571.

[111]Menguy, R. (1962). Pathogenesis of the Mann-Williamson ulcer. II, Effects of pancreatobiliary shunt to ileum on liver function of dogs, *Surgery*, 51, 616-620.

[112]Menguy, R. (1963). Pathogenesis of Mann-Williamson Ulcer. III. Effect of excluding pancreatic or biliary secretions from the intestine on gastric secretion and liver function. *Surgery*, 54, 495-502.

[113]Menguy, R., and Mings, H. (1961). Role of pancreatic and biliary juices in regulation of gastric secretion: pathogenesis of the Mann-Williamson ulcer. *Surgery*, 50, 662-667.

[114]Shimada, K., Sutter, V. L., and Finegold, S. M. (1970). Effect of bile and desoxycholate on gram negative anaerobic bacteria. *Appl. Microbiol.*, 20, 737-741.

[115]Sugawara, K., Chawla, R., and Eisenberg, M. M. (1972). Temporal relationship of gastric acid secretion to a meat meal before and after vagotomy. *Surg. Gynec. Obstet.*, 134, 307-310.

[116]Mann, F. C., and Williamson, C. S. (1923). The experimental production of peptic ulcer. *Ann. Surg.*, 77, 409-422.

[117]Storer, E. H., Schmitz, E. J., Sauvage, L. R., Kanar, E. A., Diessner, C. H., and Harkins, H. N. (1952). Gastric secretion in Heidenhain pouches following section of vagus nerves to main stomach. *Proc. Soc. exp. Biol. (N.Y.)*, 80, 325-327.

[118]Barker, W. H., and Hummel, L. E. (1939). Macrocytic anemia in association with intestinal strictures and anastomoses: Review of the literature and report of 2 new cases. *Bull. John Hopk. Hosp.*, 64, 215-256.

[119]Drasar, B. S., and Shiner, M. (1969). Studies on the intestinal flora. Part II. Bacterial flora of the small intestine in patients with gastrointestinal disorders. *Gut*, 10, 812-819.

[120]Ballinger, W. F., II, Iida, J., Padula, R. T., Aponte, G. E., Wirts, C. W., and Goldstein, F. (1965). Bacterial inflammation and denervation atrophy of the small intestine. *Surgery*, 57, 535-541.

[121]Browning, G. G., MacKay, C., and Buchan, K. A. (1969). The effect of vagotomy and drainage on bowel habit and small bowel flora in the immediate post-operative period. *Gut*, 10, 1047-1048.

[122]Greenlee, H. B., Vivit, R., Paez, J., and Dietz, A. (1970). Changes in intestinal microflora following peptic ulcer surgery. (Abstr.) *Gastroenterology*, 58, 955.

[123]Donaldson, R. M., Jr. (1970). Small bowel bacterial overgrowth. *Advanc. intern. Med.*, 16, 191-212.

[124]Hoffman, A. F. (1966). A physicochemical approach to the intraluminal phase of fat absorption. *Gastroenterology*, 50, 56-64.

[125]Goldenberg, J., and Cummins, A. J. (1963). The effect of pH on the absorption rate of glucose in the small intestine of humans. *Gastroenterology*, 45, 189-195.

[126]Dragstedt, L. R., II, Johnson, A. N., Jr., Singer, E. R., and Oberhelman, H. A. (1960). The effect of vagotomy on the intestinal phase of gastric secretion. *Surg. Forum*, 11, 336-338.

[127]Kelly, K. A., Nyhus, L. M., and Harkins, H. N. (1964). The vagal nerve and the intestinal phase of gastric secretion. *Gastroenterology*, 46, 163-166.

[128]Landor, J. H. (1964). The effect of extragastric vagotomy on Heidenhain pouch secretion in dogs. *Amer. J. dig. Dis.*, 9, 256-262.

[129]Middleton, M. D., Kelly, K. A., Nyhus, L. M., and Harkins, H. N. (1965). Selective vagal effects on the intestinal phase of gastric secretion. *Gut*, 6, 296-300.

[130]Shiina, E., and Griffith, C. A. (1969). Selective and total vagotomy without drainage: a comparative study of gastric secretion and motility in dogs. *Ann. Surg.*, 169, 326-333.

[131]Emas, S., and Grossman, M. I. (1969). Response of Heidenhain pouch to histamine, gastrin and feeding before and after truncal vagotomy in dogs. *Scand. J. Gastroent.*, 4, 497-503.

[132]Stening, G. F., and Grossman, M. I. (1970). Gastric acid response to pentagastrin and histamine after extragastric vagotomy in dogs. *Gastroenterology*, 59, 364-371.

[133]Spencer, J., and Grossman, M. I. (1971). The effect of selective gastric or extragastric vagotomy on gastric secretion in conscious cats. *Brit. J. Surg.*, 58, 489-492.

[134]Korman, M. G., Hansky, J., and Scott, P. R. (1972). Serum gastrin in duodenal ulcer. Part III. Influence of vagotomy and pylorectomy. *Gut*, 13, 39-42.

[135]Exalto, J. (1911). Ulcus jejuni nach Gastroenterostomie. *Mitt. Grenzgeb. Med. Chir.*, 23, 13-41.

[136]McCann, J. C. (1929). Experimental peptic ulcer. *Arch. Surg.*, 19, 600-659.

[137]Ivy, A. C., and Fauley, G. B. (1931). Factors concerned in determining the chronicity of ulcers in the stomach and upper intestine. *Trans. Amer. gastroent. Ass.*, 33, 81-93.

[138]Maier, H. C., and Grossman, A. (1937). Relation of duodenal regurgitation to the development of jejunal ulcers. *Surgery*, 2, 265-274.

[139]Storer, E. H., Oberhelman, H. A., Jr., Woodward, E. R., Smith, C. A., and Dragstedt, L. R. (1952). Effect of the Exalto-Mann-Williamson procedure on gastric secretion. *Arch. Surg.*, 64, 192-199.

[140]Keefer, E. B. C., Martin, K. A., and Glenn, F. (1953). A new method of producing duodenal and gastric ulcers in dogs. *Surg. Forum*, 4, 330-335.

[141]Keefer, E. B. C., Hays, D. M., Martin, K. A., Beal, J. M., and Glenn, F. (1954). Further studies of experimental gastric and duodenal ulcers in dogs. *Surg. Forum*, 5, 288-294.

[142]Baugh, C. M., Bravo, J., Dragstedt, L. R., II, and Dragstedt, L. R. (1960). The pathogenesis of the Exalto-Mann-Williamson ulcer II. Relation of the antrum to the hypersecretion of gastric juice in Mann-Williamson animals. *Gastroenterology*, 39, 330-334.

[143]Manzano, C., de la Rosa, C., Woodward, E. R., and Dragstedt, L. R. (1966). The causes of the Exalto-Mann-Williamson ulcer. *Arch. Surg.*, 93, 492-497.