

# Gastro-enterological Research

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Of all the specialties in medicine that of gastro-enterology was relatively late to develop in Sydney. Its origin, approximately two decades ago, was stimulated by the pioneering work of Sir Francis Avery Jones in London and of Dr Ian Wood in Melbourne. With the rapid rise in interest in this branch of medicine, made possible by biopsy techniques, the clinical application of biochemistry and the use of statistical methods, gastro-enterology has become in the last decade the chosen specialty of many of the outstanding medical graduates in Sydney.

The first gastro-intestinal unit in Sydney was established in 1948 at the Royal Prince Alfred Hospital under the direction of Sir William Morrow. Units were later established at the other three hospitals that serve as clinical schools for the University of Sydney; the size of these varies, as does the relative emphasis placed on clinical service, postgraduate training and research.

At the Royal North Shore Hospital my group has been concerned with the stomach and has carried on a continuing series of studies on gastric secretion, the treatment of gastric ulcer and of gastric cancer. At the Royal Prince Alfred Hospital emphasis in research has been on liver diseases and colitis, with special reference to chronic ulcerative colitis. Dr N. D. Gallagher, working in the Department on the campus, is making major contributions to the understanding of small intestine absorption. Professor C. R. B. Blackburn has had an interest for many years in portal hypertension and active chronic hepatitis but recently has been studying liver disease in New Guinea people. Goulston and Breen (1970) have recently reviewed the principal contributions of the Australian gastro-enterologists and the present article refers particularly to the interests of the Department of Medicine.

## THE STOMACH

The relationship of aspirin ingestion to gastric disease has been studied by several groups. Gillies and Skyring (1968) were able to demonstrate that the degree of association between the prevalence of chronic gastric ulcer and aspirin ingestion suggested a causal relationship. In the same unit, Goulston and Cooke (1968) showed that alcohol ingestion with unbuffered aspirin resulted in greater faecal blood loss than unbuffered aspirin alone, although alcohol alone did not cause gastro-intestinal bleeding.

In a study of the natural history of benign gastric ulcer, 90 patients with benign ulcer admitted to the Royal North Shore Hospital for medical treatment over a 3½-year period were reviewed retrospectively (Herrmann and Piper, 1970). Healing rate was measured by using profile surface area air contrast radiography of the stomach every 21 days.

Ulcer size was found to be greater in those who smoked cigarettes or gave a history of ingestion of salicylate-containing compounds. Healing rate was accelerated by admission to hospital, but was uninfluenced by the age or sex of the patient, positive family history of gastric ulcer, duration of ulcer symptoms prior to admission, number of recurrences of therapy with frequent doses of potent antacids. Healing rate was retarded in those who took salicylate-containing preparations even after they ceased taking them.

In a series of studies on the treatment of gastric ulcer, Piper's group has examined some pharmacological agents or other agents assumed to have beneficial effects on the healing ulcer. The dosage of antacid needed effectively to neutralise gastric juice at various acid secretory rates was calculated mathematically from available physiological data (Myhill and Piper, 1964; Piper and Fenton, 1964). Subsequently, these doses of antacid, as calcium carbonate, were subjected to double blind clinical trial. These therapeutic regimes did not influence the healing rate of chronic gastric ulcer in ambulant patients (Baume and Hunt, 1966) despite an incidence of hypercalcaemia of approximately 30 per cent (Stiel *et al.*, 1967). Anti-cholinergic drugs reduced gastric acid secretion but the pH of the gastric content was not altered and mucus concentration rose (Piper and Stiel, 1961; Piper *et al.*, 1962a). Double blind clinical trials have shown that the anti-cholinergic drug glycopyrrolium bromide accelerates the healing rate of gastric ulcer in patients treated in hospital and reduces the recurrence rate in patients whose ulcer had been healed and who were treated as outpatients (Baume *et al.*, 1970).

These studies were greatly facilitated by the use of air contrast gastric radiography developed from the pioneer work of the Japanese (Shirakabe, 1966). Using this technique, small ulcer craters and early mucosal deformities associated with gastric cancer can more readily be detected (Fig. 1). It is also much easier to measure the size of a gastric ulcer.

It appears that some of the new proprietary anti-cholinergic drugs have a selective action on the stomach superior to that of atropine, and a series of such drugs has been tested for selective action on gastric secretion. Equipotent doses of oxyphencyclamine and of atropine were determined in patients by measuring their effect on saliva flow and constructing dose response curves. Subsequently, equipotent doses as regards saliva flow were administered to the same subjects and gastric secretion measured. It was found that oxy-

phencyclamine had a more potent effect on gastric secretion than atropine in six of the seven subjects studied. This is the first time selectivity has been demonstrated for the newer anticholinergic drugs using pharmacologically acceptable techniques (Herrmann and Piper, 1970).

The investigation of gastric secretion has concerned the search for secretory abnormalities associated with peptic ulcer and gastric cancer, especially an exploitable biochemical lesion that would facilitate the diagnosis of these two diseases (Piper, 1968). Simultaneously with Swedish workers, the techniques of intragastric neutralisation were introduced, thereby enabling the proteins and enzymes in gastric juice to be studied unaltered by the indeterminate variables of peptic digestion and acid denaturation (Piper *et al.*, 1962b; Piper, 1968).

An increased  $\beta$ -glucuronidase activity has been found in the gastric secretions of 70 per cent of patients with gastric carcinoma and a special study has been made of those who do not have this increase. A  $\beta$ -glucuronidase inhibitor has been found in human gastric juice. This inhibitor is heat stable and partially dialysable and is thought to be a sulphated polysaccharide.

A lactic acidosis in gastric juice has been found in 60 per cent of patients with gastric carcinoma and 1 per cent of patients without it. It is possible that the lactic acidosis in gastric juice reflects a biochemical lesion in the gastric mucosal cells predisposing the patient to gastric cancer and may be a reflexion of a disorder of pyruvate metabolism in cancer (Piper *et al.*, 1970b).

Attempts have been made to increase the lactic acid concentration of gastric juice by massive infusions of glucose, fructose and epinephrine and the first two often caused a marked rise in the lactic acid concentration of gastric juice. Those persons who failed to show a rise in the lactic acid content of gastric juice probably had their response restricted by rate limiting enzymes along the fructose-lactic acid pathway.

In the search for abnormal proteases that may play a part in peptic ulcer, it has been shown, using high voltage gel electrophoresis, that human pepsinogen can be separated into six isoenzymes (Piper *et al.*, 1970a). In case the absence of a protease inhibitor might be the causal circumstance in the aetiology of peptic ulcer, an investigation of protease inhibitors in the mucosa of patients with and without ulcers was carried out. Although a weak protease inhibitor was found in normal gastric mucosa, its activity was unrelated to ulcero-genesis and it was found in other tissues such as muscle. Studies of gastric mucus from patients with peptic ulcer, gastric cancer and pernicious anaemia have shown that it does not differ from gastric mucus from normal subjects as regards its concentration, output and constituent sugars (Piper *et al.*, 1965); however, the mucus from patients with peptic

ulcer, especially duodenal ulcer, has a significantly increased capacity to bind the dye alcian blue (Piper *et al.*, 1970c).

#### THE SMALL INTESTINE

Gallagher (1969) used the neonatal rat to study the intrinsic factor dependent transport of Vitamin B<sub>12</sub> and has shown that the neonatal rat is able to absorb Vitamin B<sub>12</sub> independently of intrinsic factor and that transport across the wall of the ileum is enzymatic and obeys Michaelis–Menten kinetics. The vitamin is carried across the mucosa by a specific transport system which can be interfered with by the simultaneous feeding of analogues which have defined substitutions in appropriate parts of the Vitamin B<sub>12</sub> molecule (Foley and Gallagher, 1969).

The transition from intrinsic factor independent, i.e. pinocytosis, to intrinsic factor dependent absorption of Vitamin B<sub>12</sub> occurs at the end of the third week of life, coinciding with the maturation of the ileal epithelium. The administration of cortisone to ten-day-old rats increased the amount of intrinsic factor to the level found in older rats, converted the ileum to the adult form and changed the absorption of Vitamin B<sub>12</sub> to the adult intrinsic factor dependent type (Gallagher and Foley, 1970a).

In similar studies it was shown that the control of iron absorption and transport in young rats differed from that found in adult rats and that there are two mechanisms of iron absorption in young rats—carrier mediated and pinocytic (Gallagher and Foley, 1970b).

Posen and his colleagues have shown that the intestine makes a significant contribution to the total body pool of alkaline phosphatase. In the adult, intestinal alkaline phosphatase accounts for approximately 20 per cent of the circulating phosphatase after a fatty meal (Kleerekoper *et al.*, 1970). In the rat, the contribution from the intestine is greater than in the human (Saini and Posen, 1969).

#### THE COLON

Goulston and the group at the Royal Prince Alfred Hospital have maintained an active interest in the disorders of the colon and their major interests have been in chronic ulcerative colitis, Crohn's disease and ischaemic colitis (Goulston and Breen, 1970).

In a series of papers Goulston and his colleagues (Boden *et al.*, 1959; Mistilis and Goulston, 1965; Mistilis *et al.*, 1965) have drawn attention to the frequent occurrence of pericholangitis in patients with ulcerative colitis and that the course of this lesion does not appear to be altered by antibiotics, steroids or colectomy.

The frequency of occurrence of ischaemic entero-colitis, a specific condition, in the older person, especially after an episode of hypertension (from drugs, haemorrhage, or myocardial infarction), in uraemia and in septicaemia has been emphasised by McGovern and Goulston (1965) and attention drawn to the way in which it may be differentiated from ischaemic colitis due to large internal occlusion (Goulston and McGovern, 1968).

#### THE LIVER

The group in the gastro-enterology unit at Royal Prince Alfred Hospital has had a continuing interest in liver disease. There has been a particularly active programme involving the clinical and pathological study of patients with active chronic hepatitis on a long term basis and a number of joint hospital-university publications have appeared.

The clinical features of active chronic hepatitis (active juvenile cirrhosis, lupoid hepatitis, plasma cell hepatitis) have been defined by Mistilis and Blackburn (1970). They found in a study of 86 patients that 80 per cent were female; the age of onset was usually between 16 years and 30 years and in one third the onset was abrupt and indistinguishable from acute viral hepatitis. Clinically two or more of the following symptoms were usually present: slow progressive jaundice, anorexia, hepatomegaly, abdominal pain, epistaxis, acne, fever and arthralgia. Recurrent episodes of active liver disease punctuated the course of the illness. Without therapy, 65 per cent were dead by the end of five years, the cumulative survival being only slightly better than that of a group of patients with cirrhosis due to other causes. The important role of liver biopsy, where perilobular parenchymal necrosis and degeneration are the major features, was stressed. Though steroids, 6 mercaptopurine and azothioprine did not alter the overall survival, they produced biochemical and clinical improvement and were effective in reducing the mortality early in the course of the illness.

For many years steroids and 6 mercaptopurine or azothioprine have been used for treatment and excellent results have been reported (Arter *et al.*, 1966; Mistilis and Blackburn, 1970) especially in decreasing the dose of steroids and the distressing adverse effects so often seen in young women. Several patients now have no abnormalities of liver function and quite inactive disease as judged by liver biopsy.

Studies directed at the pathogenesis of Wilson's disease using adult and neonatal rats (Mistilis and Farrer, 1968; Mearrick and Mistilis, 1969; Farrer and Mistilis, 1967; Mistilis and Mearrick, 1969) have shown that maintenance of low body copper in the adult is achieved by the excretion of

copper in bile in the form that prevents its subsequent absorption and promotes its excretion.

Mistilis and Garske (1969) showed that alcohol liver dehydrogenase and lactic dehydrogenase were present in the stomach and small intestine and both enzymes could be induced by acute and chronic alcohol feeding. Mistilis *et al.* 1965 demonstrated for the first time that there was retrograde flow of intestinal lymph into the intestine lumen in cases of intestinal lymphangiectasia.

Kater and Mistilis (1967) have shown that the syndrome of pruritis of pregnancy is simply a variant of obstetric cholestasis with similar biochemical tests of hepatic function, transport maximum and the hepatic storage of BSP.

As the result of a continuing interest in portal hypertension, a group of physicians and surgeons have worked together and obtained excellent surgical results (Stathers *et al.*, 1968). Spleno-renal veno-venous anastomoses are preferred to portacaval ones and it is a matter of policy that a satisfactory flow through the shunt shall be recorded by venography before the abdomen is closed. It has been rare to see patients develop encephalopathy after a spleno-renal shunt except as the result of advanced liver disease. A small post-mortem series has demonstrated that most shunts remain patent. Conservative management is recommended more frequently now than five or ten years ago and exclusion of all forms of salicylate and of traumatic dietary items results in a marked decline in bleeding episodes.

Ma *et al.* (1969) reported the successful substitution of lactulose for neomycin in the long term management of chronic portal-systemic encephalopathy. Latterly several of their patients who would not take lactulose have developed disabling ototoxicity from long-term neomycin in the presence of renal functional impairment.

Goldstein (1970) has studied three patients with splenic vein thrombosis, gastric varices and severe bleeding episodes. Two patients had chronic pancreatitis but one had a chronic gastric ulcer which had penetrated through the stomach wall. Arteriography and splenopatology were diagnosed in all three patients who have been relieved or cured of their bleeding by splenectomy.

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