Gastroenterology in the armed forces

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Sir Christopher Booth has a long association with the armed forces, beginning with wartime service in the Royal Navy. In the 60s he was closely involved in the investigation of tropical sprue in British soldiers in the Far East. In the early 70s he was appointed a Civil Consultant to the Royal Navy and joined the Royal Naval Clinical Research Working Party, evaluating the scientific content and ethics of all clinical research within the service; he continues to give invaluable help on the committee which now fulfils the same function and has been associated with virtually all the naval work described in this review. In 1984 he took on the additional task of chairmanship of the Royal Naval Personnel Research Committee of the Medical Research Council. His concerns for service medicine in general and service gastroenterology in particular are therefore of long standing.

Gastrointestinal disease has been a problem for sailors and soldiers since time immemorial. Drake died of dysentery and this was still a common problem at sea and ashore by the 18th century. By that time, however, the great James Lind, who had devised the first clinical trial,1 was able to observe that sailors in the fleet were healthier afloat than landsmen ashore. This may well have been true as scurvy, typhus, and dysentery were endemic in England and among soldiers everywhere. In the 20th century duodenal ulcer (DU) emerged as a major cause of morbidity in servicemen, while diarrhoeas of various causes continued to be a serious problem in soldiers serving abroad.

Tropical sprue

Sprue, which had first been described by Ballingal, a young medical officer in the army in 1818,1 had been a major cause of invaliding of servicemen from the South East Asia command during the Second World War, and the problem was extensively studied by medical officers in the Royal Army Medical Corps and the Indian Medical Service. They had defined the clinical syndromes but were divided as to whether sprue was a deficiency disease or one of infective origin.14 With the advent of small intestinal biopsy,17 and cobalt labelling of vitamin B1212 the whole problem was studied in greater depth and Booth was able to classify the malabsorption syndrome in the light of a new understanding of the pathophysiology.10

In 1961, as a result of an initiative by the Wellcome Trust which was already supporting work on tropical sprue by Dr Selwyn Baker and others at Vellore, South India, a collaborative study of tropical metabolic disorders was set up in four centres. These included the British Military Hospital, Singapore (Colonel William O'Brien and Lieut Col Norman England) and the Royal Postgraduate Medical School at Hammersmith (Dr Christopher Booth and Dr David Mollin). The timing of this initiative was particularly opportune as far as the British Army were concerned, for it coincided with operations in Borneo where troops were living in the jungle on pack rations, circumstances that had been associated with severe outbreaks of sprue during the Second World War. As far as the Army were concerned, Christopher Booth and David Mollin were closely involved in the planning of the studies, made investigatory facilities available and continued to provide close and enthusiastic supervision.

At the Hammersmith, Booth and Mollin described a syndrome of chronic tropical sprue in expatriates who, after a number of years of untreated sprue developed profound vitamin B12 deficiency with a severe enteropathy. In contrast, O’Brien and England in Singapore and later at the RAMC College at Millbank, London, defined a consistent clinicopathological syndrome in previously fit young men. In early cases of a few weeks duration, they showed that there was malabsorption of fat, D-xylose and vitamin B12. Folate deficiency was a constant feature with minimal megaloblasticosis but jejunal mucosal changes were slight. The disease in those who had suffered for longer was characterised by evidence of increasing vitamin B12 deficiency related to the duration of symptoms; in addition there was mild to moderate megaloblastic anaemia. The jejunal mucosa showed a characteristic appearance which was related to the duration of the disease and there was close correlation between the dissecting microscope appearances and the histological changes and between the mucosal appearances and the severity of the malabsorption. In many cases the illness appeared to be infective in origin and in all cases the development of both intestinal and haematological abnormalities were related to folate status. There was a partial response to folate treatment, particularly in those whose symptoms were of short duration and a complete cure
when broad spectrum antibacterial drugs used in addition. All the patients in these series made a complete recovery and the service personnel returned to active duty.\textsuperscript{16}

With the withdrawal of British military interests from East of Suez, sprue in soldiers has become a rarity. It is probably true to say that our understanding of tropical sprue has advanced little since these studies were undertaken but it seems likely that the clinical picture represents an end point of a variety of aetiological factors.

**Constipation and Diarrhoea**

It would be inappropriate to omit from a review such as this the work of Surgeon Captain T L Cleave. His original letter noting the beneficial effects of bran in constipated sailors in the battleship King George V,\textsuperscript{11} passed almost unnoticed, but the significance of dietary fibre has now been appreciated by a new generation of gastroenterologists. In the investigation of unusual diarrhoeas, Roberts and colleagues reported some early studies with the electron microscope on two patients with Whipple's disease diagnosed at jejunal biopsy by the British Military Hospital, Munster. The bacteria in the lamina propria had disappeared after treatment with either chloramphenicol or ampicillin.\textsuperscript{12,13}

**Dyspepsia and peptic ulcer**

During the Second World War Rae had observed that one third of all invalidings from the Royal Navy were the result of peptic ulcer (PU) disease.\textsuperscript{14} Sir Arthur Hurst believed that an enormous saving of manpower for both the Army and civilian services would result from establishment of specialised units for gastrointestinal disease.\textsuperscript{15} Watt reviewed the aetiology and incidence of PU in the Royal Navy and found that the incidence of PU in the period 1959–68 was nearly twice that of men in the civilian population, and that it rose throughout the decade.\textsuperscript{16} By the 1970s, however, the incidence of DU was falling slowly while, as a result of therapeutic advances, days lost to the Royal Navy and invalidings from the service fell dramatically.\textsuperscript{17}

That the lifestyles of soldiers and sailors contributed to their symptoms has been believed for centuries. Watt had shown that consumption of spirits was significantly higher among sailors than among a control group, as was smoking and the consumption of refined carbohydrate.\textsuperscript{18} The advent of new techniques has allowed scientific study of this hypothesis during the past 30 years. Roberts, using the Crosby capsule, performed gastric biopsies in 56 soldiers who were either alcoholics or heavy drinkers and found a correlation between the duration of excessive alcohol ingestion and histological evidence of chronic gastritis, while histological change was infrequent in controls without a history of alcohol excess.\textsuperscript{19}

Two major events in gastroenterology determined the direction of gastroenterological research in the armed forces during the 1970s: first, as a result of the development of fibreoptic technology and its application to visualisation of the foregut, colon and pancreaticobiliary tracts, endoscopy became a practical tool for the investigation of patients. It provided more precise criteria for healing of peptic ulcers than had hitherto been possible. Second, a major therapeutic breakthrough occurred with the definition of histamine H\textsubscript{2}-receptors by Black and his colleagues.\textsuperscript{20} Here, endoscopy allowed better evaluation of the therapeutic agents that were to be developed as a result of Black's new concept.

A joint group drawn from the Royal Navy and the MRC unit at the Central Middlesex Hospital had been set up in 1971 to study the intestinal effects of prostaglandins on the intestine by motility and perfusion techniques and work had been done with prostaglandin F\textsubscript{2α} and E\textsubscript{2}.\textsuperscript{21,22} In 1973, by courtesy of Smith, Kline, and French, the group was able to study the second generation histamine H\textsubscript{2}-receptor antagonist metiamide. Eleven patients with DU were given a single dose on retiring and acid secretion was studied overnight. Ten of these responded to the drug with a highly significant reduction of gastric acid secretion and eight of these were rendered anacidic for varying periods.\textsuperscript{23} On the basis of these exciting data, a controlled trial was begun in which patients with DU were treated with either metiamide 1 g daily by mouth or placebo and symptoms assessed. There were significant reductions in nocturnal pain and antacid consumption but the trial was terminated after 30 patients had been studied when reports were received from elsewhere of granulocytopenia.\textsuperscript{24} Shortly after this, cimetidine became available to the group and clinical pharmacological studies were undertaken, using food induced gastric acid secretion in normal male volunteers as the experimental model. Cimetidine 200 mg inhibited food stimulated acid secretion by 67% when taken half an hour before meals and by 57% when taken with food.\textsuperscript{21} Roy Pounder, who had by then joined the group as a research fellow, conceived the idea of monitoring intragastric hydrogen ion activity over a 24-hour period, thus allowing the effect of an anti-secretory drug to be studied under near physiological conditions for relatively prolonged periods. In 1975 the effect of H\textsubscript{2}-receptor blockade with cimetidine was studied in nine healthy male volunteers at the Royal Naval Hospital, Plymouth.\textsuperscript{25} The pH of the
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gastric contents was measured hourly by day and two hourly by night while the subjects ate regular meals, drank identical volumes of fluid and smoked the same number of cigarettes at the same time on two study days. During one of these days placebo was administered, on the other, cimetidine 0-8-1-0 g. Replicate placebo studies in an additional subject gave good reproducibility. Mean hydrogen ion activity was inhibited by 70% (p <0-01). Using the same technique, six patients with DU were studied comparing two different doses of cimetidine, 0-8 g/day and 1-2 g/day. The lower dose inhibited intragastric acidity by 55%, the higher by 67%, the difference being most marked at night.26 On the basis of these findings the original dose for cimetidine in the UK was established and therapeutic trials were initiated widely.

The rationale for treating gastric ulcer (GU) with H₂-receptor antagonists seemed less certain, but an open trial of cimetidine in 10 patients with GU resulted in the healing of all within six weeks.27 Carbenoxolone was, at the time, the drug most widely used in the treatment of GU, and a comparative trial of cimetidine against carbenoxolone was carried out in which 54 patients with GU were treated with one or other drug. A therapeutic gain of 26% was shown for cimetidine but the difference was not significant,28 and other trials showed no advantage for either regimen.

Inevitably, comparisons were also made with other therapeutic regimens in DU. Using the 24-hour technique a comparison was made between high dose antacid therapy at that time popular in the USA, cimetidine and placebo in DU patients. This showed that high dose antacid caused a highly significant reduction in intragastric pH which was comparable with cimetidine as long as therapy was administered, but the effect was less after midnight.29 With the same technique, patients with DU due to undergone proximal gastric vagotomy (PGV) were studied with the standard dosage of cimetidine and also a placebo day preoperatively, and a further placebo day six months after surgery. These results showed that PGV was more effective in lowering intragastric hydrogen ion activity than was cimetidine, but the morbidity of surgery was perceived to be a disadvantage.30 The possibility of potentiation of cimetidine by anticholinergics was studied by comparing the effect of oral administration of cimetidine and atropine, in combination and separately, with placebo using the 24 hour technique. The data showed that atropine in the maximum dose which avoided definite unwanted effects (2-4 g/day in divided dosage) had no significant additive or potentiating effect on 24 hour intragastric acidity.31 More recently, the effects of adding pirenzepine, a selective inhibitor of type 1 muscarinic receptors in vagal ganglia, were studied when administered separately to and in combination with cimetidine in patients with DU. Pirenzepine in combination with cimetidine was significantly better over the 24 hour period than either cimetidine or pirenzepine alone, but it was believed that it would be necessary to administer the drugs in combination three times daily to achieve an adequate reduction in intragastric acidity over the 24 hour period.32

Effects of cimetidine therapy which might prove unwelcome were also studied. The effect of the drug on pentagastrin stimulated intrinsic factor (IF) production was studied in healthy volunteers. While IF output was significantly reduced in response to cimetidine, IF concentration in gastric juice was unchanged, suggesting that the change was a factor of reduction in volume.33 The substantial effect on intragastric pH in patients treated with cimetidine raised the question of whether the drug might be carcinogenic. Two possibilities were proposed. One was that cimetidine might be nitrosated in vivo, the resultant nitroso derivative being carcinogenic. Nitroso-cimetidine, in numerous animal studies, had not shown such characteristics, and the alternative seemed more likely. This hypothesis, that the rise in pH created a different intragastric milieu in which nitrate reducing bacteria flourished and N-nitroso compounds were formed was investigated at the Royal Naval Hospital, Haslar. Normal and DU patients were studied in four separate 24 hour periods. Gastric juice was measured for pH, nitrite, and total and stable nitroso compounds; bacteriological studies identified the range of species and the presence or absence of nitrate reducing bacteria. As predicted, cimetidine increased pH, but there was no significant effect on nitrite production or on the concentration of stable or total nitroso compounds. Nitrate reducing bacteria were able to proliferate for short periods but colonisation did not occur.34

The advent of new H₂-receptor antagonists, notably ranitidine (Glaxo), provided further opportunities for clinical pharmacology and this new compound was studied using techniques essentially similar to those developed for cimetidine. In a comparative study of the effects of ranitidine (150 mg or 200 mg bd), cimetidine (200 mg tid and 400 mg nocte) and placebo on 24 hour intragastric acidity, it was shown that the degree of inhibition with ranitidine 150 mg bd was significantly greater than that with cimetidine 1 g/day, but that ranitidine 200 mg bd conferred no additional advantage.35 Subsequent therapeutic trials comparing ranitidine with the standard dosage of cimetidine then in use (1 g/day) in 103 patients showed no significant advantage to either drug in either symptomatic relief or endoscopic healing after four weeks of therapy.36 Main-
tenance therapy with ranitidine 150 mg nocte was also found to have no advantage over cimetidine 400 mg nocte in a multicentre study of 61 patients but these findings were not borne out by another, larger study. At this time an interesting new pharmacological tool was developed at Smith Kline and French: Impromidine, a specific agonist for the histamine H₂-receptor. This was studied in depth at the Royal Naval Hospital, Haslar, where its effects were assessed in healthy volunteers both as a secretagogue and in its capacity to be blocked by cimetidine and by oxmetidine. The desire to inhibit gastric acid secretion over a longer period at less inconvenience to the patient, and therefore with better compliance, resulted in a search for longer acting H₂-receptor antagonists and, when these proved elusive, in a reassessment of dosage regimens. Oxmetidine (Smith, Kline & French), was studied extensively during the latter part of the 1970s. It was certainly two to four times more potent than cimetidine on a molar basis depending on the experimental model used, but was not longer acting. In terms of duration of action SK&F 93479 was considerably longer than cimetidine, and dose ranging studies on the 24 hour intragastric acidity model were looking promising when it too showed signs of toxicity in longterm animal studies. The tendency for a number of long acting H₂-receptor antagonists to prove toxic in longterm animal toxicity studies encouraged the alternative approach of using larger doses of compounds well established as safe, in order to achieve prolonged activity. The effects of two dose regimens of cimetidine, 400 mg bd or 300 mg nocte, and two of ranitidine 150 mg bd or 300 mg nocte were assessed over 24 hour periods, and no significant difference was seen between the dosage regimens with either drug. In another study, large single doses of cimetidine ranging from 800 mg to 1600 mg were given at either 1800, when they were compared with ranitidine 300 mg, or at 2300, when intragastric acidity and nocturnal acid and pepsin output were studied against placebo over successive 24 hour periods. A dose related reduction in intragastric acidity was seen, inhibition of peptic activity was less when the drugs were administered at 1800 and cimetidine 1600 mg and ranitidine 300 mg were similar in their effects. A multicentre trial including the Royal Naval Hospital, Haslar, studied 102 patients with endoscopically proven DU, comparing treatment with ranitidine 150 mg bd with ranitidine 300 mg nocte. Healing rates were as good with the higher single dose of ranitidine as with the divided dose regimen. The accumulation of large quantities of data on intragastric acidity in DU patients both on placebo and on cimetidine 1 g/day prompted Dr Roger Pethybridge, statistician at the Institute of Naval Medicine, to observe that there appeared to be two varieties of response to cimetidine, which could be separated by the hydrogen ion activity overnight. This phenomenon was studied at Haslar by Hunt, who defined responders as those with an intragastric hydrogen ion activity at 0300 of less than 5 mmol/l, those with a higher level being non-responders. Nineteen of 36 DU patients studied were responders, while all non-responders had levels above 11.5 mmol/l. Analysis of placebo hydrogen ion activity showed no difference between these two groups during the day, but a significant difference overnight (p<0.05). The observed differences were difficult to explain, but were not the result of poor absorption of the drug, for blood concentrations in the two groups were comparable. Of the six who subsequently underwent PGV, three came from each group, but the end result of surgery showed no significant differences between the two groups in terms of overnight acid output and both were all classified as Visick grades I or II. Different groups of patients with DU and a poor clinical and endoscopic response to cimetidine were then studied at Haslar over separate 24 hour periods, receiving no treatment, cimetidine 1 g/day, cimetidine 2 g/day or cimetidine 1 g/day together with atropine 4-8 mg/day. Despite adequate absorption, cimetidine had a decreased effect on gastric acid secretion in the poor responders and increasing the dosage of drug did not improve response. Control of acid output was, however, dramatically improved when cimetidine was combined with atropine. Studies of nocturnal acid secretion in refractory DU patients, however, suggested that very high doses of cimetidine, 1600 mg at night were more effective in achieving ulcer healing than cimetidine 400 mg given with pirenzepine 50 mg. These studies leave the question of poor response to H₂-receptor antagonists unresolved. It appears that there is a vagal component to gastric secretion not readily amenable to inhibition by H₂-receptor antagonists. There is evidence that peptic activity is more important than had at first been supposed, but further work remains to be done. The ease with which servicemen have access to tobacco, and the fact that, until recently, there was no climate of opinion against the habit, allowed Hull and Beale to study 70 cigarette smokers with endoscopically proven DU. After treatment with a standard course of cimetidine and advice to cease smoking there was a significantly higher relapse rate at six months among those who had continued to smoke.
working both with David Johnston at Leeds and subsequently at Haslar, compared the results of highly selective vagotomy (HGV) with traditional operations for peptic ulcer. They showed that reflux gastritis as measured by bile acid concentrations (BAC) and lyssolecithins in the stomach was significantly less after HGV than after traditional gastric surgery. Among patients presenting at Haslar with bleeding or perforation of a peptic ulcer, 50% of those requiring emergency surgery had a recent history of ingestion of non-steroidal anti-inflammatory drugs (NSAID), the figures confirming other series in which the risks of taking NSAIDs are particularly high among elderly women.

Colonoscopy

Swarbrick and colleagues working at St Mark’s Hospital in the early days of colonoscopy, had demonstrated its superiority over radiology in the diagnosis of radiograph negative rectal bleeding when a survey of colonoscopies in 239 patients with unexplained, radiograph negative rectal bleeding. A cause for bleeding was found in 95 patients, of whom 23 had carcinomas. This multicentre series, which included Richard Hunt’s data from Haslar, became increasingly large over the years, while the relative incidence of pathology undetected by radiology remained remarkably constant.

At Haslar, the decision was made at an early stage to concentrate on developing expertise on upper GI endoscopy and on colonoscopy, leaving cannulation of the biliary and pancreatic ducts to others. Through the 1970s, the era of ‘self teaching’ was accompanied by surprisingly few complications, but those days are now over and the need for adequate and detailed supervision has been recognised by the British Society of Gastroenterology. The whole question of safety in colonoscopy has been reviewed by Hunt.

Conclusion

This review has concentrated on some of the research done in the armed forces which has been directed at specific clinical problems common among service men. It is often assumed that experiments using human volunteers and patients are easier in a disciplined service; one still hears the music hall jibe of ‘You, you and you!’. In the sense that servicemen are accustomed to do what they are told, are punctual and reliable, and that, for them, it is a point of honour to endure discomfort without complaint, it is indeed easier. But those conducting research in the armed forces must be, for these very reasons, particularly careful about the need for genuinely informed consent by those volunteering to be experimental subjects. Tight ethical and scientific supervision of clinical research has been obligatory in the Royal Navy, for example, for 25 years, and it is in this area that we owe a particular debt to Sir Christopher Booth.

I am particularly grateful to my former colleagues, Surgeon Commander Richard Hunt RN Retd and Surgeon Commander John Williams RN Retd for reminding me of the work we did together. I am also most grateful to Major Generals Bill O’Brien and David Roberts, to Brigadier Norman England and to Air Commodore David Hull RAF for their help in compiling this review.

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