PAPERS AND SHORT REPORTS

Highly selective vagotomy and duodenal ulcers that fail to respond to H_2 receptor antagonists

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Abstract

A study was conducted to see whether patients with duodenal ulcers that failed to heal in response to H_2 receptor antagonists had a higher incidence of recurrent ulceration after highly selective vagotomy than patients whose ulcers healed with these drugs. Between 1977 and 1983, 157 patients had a highly selective vagotomy for uncomplicated duodenal ulcer; in 57 patients the ulcer had failed to heal despite treatment with H_2 receptor antagonists (refractory group), 19 patients had developed recurrent ulceration while receiving maintenance treatment, 67 patients had remained healed while taking H_2 receptor antagonists but suffered frequent relapses when treatment was stopped, and 14 patients had not been given these drugs before operation. The overall incidence of recurrent ulceration was 6% after two years and 11% after five years of follow up. In the refractory group, however, the incidence of recurrent ulceration was 18% at two years and 34% after five years, whereas the incidence of recurrence was only 1·5% at two years and 3% after five years in patients whose ulcers had healed with H_2 receptor antagonists. Resistance to H_2 receptor antagonists was not related to preoperative basal or peak acid output but was related to cigarette smoking. Factors associated with recurrent ulceration after highly selective vagotomy were basal acid outputs before and after operation, cigarette smoking, and the surgeon who performed the operation.

Duodenal ulcers that fail to respond to H_2 receptor antagonists represent a more severe ulcer diathesis, for which highly selective vagotomy is less effective.

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Introduction

The H_2 receptor antagonists cimetidine and ranitidine have revolutionised the management of duodenal ulceration. They are very effective in healing duodenal ulcers, endoscopic healing rates of over 80% readily being achieved after six weeks.[1] There is a subgroup of patients, however, whose ulcers fail to respond even to these potent drugs. By definition a duodenal ulcer that fails to heal after three months of treatment is termed "refractory."[2] Though such ulcers sometimes heal if treatment with H_2 receptor antagonists is continued for longer, or in response to other drugs such as mucosal barrier agents,[3] these patients represent a problem in management for gastroenterologists and are frequently referred for surgical treatment.

Apart from refractory duodenal ulcers there are other categories of failure with H_2 receptor antagonists. Some patients have ulcers that heal with full dosage of the drugs but recur during maintenance treatment, usually given as a single night time dose of 400 mg cimetidine or 150 mg ranitidine. Other patients remain healed during maintenance treatment but suffer frequent, rapid, and troublesome relapses when treatment is stopped. Because either the patient or the physician is unwilling to continue treatment for life, these patients with "relative" failure of H_2 receptor antagonists may also be referred for surgery.

Highly selective vagotomy is the safest operation for duodenal ulceration[4] and has the fewest side effects.[5-8] Incidences of recurrent ulceration ranging from 2% to 30% have been reported five to eight years after highly selective vagotomy,[6 9] but when the procedure has been carried out by experienced surgeons using standard techniques an incidence of recurrent ulceration of 5-10% after five years has often been achieved.[5 6 10 11] Many of these studies, however, were begun or even completed before H_2 receptor antagonists became widely available and thus before failure of response to H_2 receptor antagonists became the main criterion for selection of patients for operation.

The aim of this study was to determine the effectiveness of highly selective vagotomy for patients with duodenal ulceration who belonged to various categories of response to H_2 receptor antagonists. In particular we wished to know whether ulcers that had failed to heal in response to these drugs would heal and remain healed after highly selective vagotomy.

Patients and methods

One hundred and fifty seven patients with duodenal ulceration were operated on electively between 1977 and 1983. No other gastrointestinal disease was present. Each patient had gastric secretory studies performed before and after operation. All except 14 patients had received H_2 receptor antagonists before operation. For this study "full dose" treatment was defined as cimetidine 200 mg four times a day plus 400 mg at night or ranitidine 150 mg twice daily. The response to H_2 receptor antagonists before operation was determined and the patient placed in one of the following four categories.

Refractory ulcer—Patients with refractory duodenal ulcers had failed to obtain an adequate symptomatic response to three months of H_2 receptor antagonist in full dosage and were found to have persistent ulceration at gastroduodenoscopy. Many patients were referred for surgery at this stage while others continued with medical treatment for a variable period, but in none did the ulcer heal. These patients thus represent the extreme end of the range of resistant duodenal ulcer disease.

Relapse during maintenance treatment—Patients who relapsed during maintenance treatment had obtained a good symptomatic response within three months of beginning H_2 receptor antagonist in full dosage but healing was not invariably checked by gastroscopy. Symptomatic recurrence occurred while they were receiving maintenance treatment and in each case recurrent ulceration was confirmed endoscopically.

Healed with H_2 receptor antagonists—Patients who healed with H_2 receptor antagonists had obtained a good symptomatic response to both the full dose of the drug and subsequent maintenance treatment. They were referred for surgical treatment because of troublesome relapses of symptoms when treatment was stopped, and recurrence of the ulcer was confirmed endoscopically. As healing was not always checked by gastroscopy when patients were asymptomatic, possibly some both in this group and the group who relapsed during maintenance treatment had asymptomatic but unhealed ulcers at some stage in their treatment. They may therefore have been more "refractory" than their classification suggests.

No H_2 receptor antagonists—Fourteen patients were operated on without receiving treatment with H_2 receptor antagonists. Operations were elective but usually for an acute complication of duodenal ulcer disease such as haematemesis or melaena, surgical treatment being preferred to reduce the likelihood of further complications.

Of the 157 patients, 57 had ulcers refractory to H_2 receptor antagonists, 19 had relapsed during maintenance treatment, 67 patients had healed with H_2 receptor antagonists but were operated on for frequent, troublesome relapses, and 14 patients had never received H_2 receptor antagonists. The groups were similar with respect to age, sex, and body weight, with the exception of the fourth group, which consisted entirely of men (table I).

Tests of gastric secretion—Each patient had a combined insulin-pentagastrin test[12,13] before and one week after operation. The insulin component of the test was omitted if the patient was over 65 or suffered from ischaemic heart disease, diabetes, or epilepsy.

Operation and follow up—The operative technique of highly selective vagotomy was as described.[14,15] The surgeon was either a consultant or senior registrar and well versed in the technique. A few operations were performed by registrars under the supervision of a more senior surgeon. Patients were followed up at a gastric follow up clinic and assessed "blind" by a physician and surgeon without reference to the operative procedure or preoperative response to H_2 receptor antagonists. Patients were reviewed twice in the first year and yearly thereafter. Any patient who complained of dyspepsia was investigated by upper gastrointestinal endoscopy, but endoscopy was not performed routinely to exclude asymptomatic recurrence.

Statistical analysis—The incidence of recurrent ulceration was calculated for all patients and for each subgroup of patients from one to five years after highly selective vagotomy by life table analysis. Calculations were based on the number of recurrences and the number of patients who attended for follow up.[16] Statistical comparisons were by the log rank test, Mann-Whitney U test, and χ^2 test, as appropriate.

Results

Mortality—There was no operative mortality, nor was there any mortality related to peptic ulceration in the follow up period. No reoperations were required in the early postoperative period.

Recurrent ulceration—During the follow up period of between three and nine years 14 of the 157 patients suffered recurrent pyloroduodenal ulceration; no patient developed a gastric ulcer. The distribution of recurrent ulcers was 11 among the 57 patients in the refractory group, none among the 19 who relapsed while receiving maintenance treatment, two among the 67 who healed with H_2 receptor antagonists, and one among the 14 patients who had not received an H_2 receptor antagonist. Recurrent ulceration was more frequent in the refractory group than in the group who healed with H_2 receptor antagonists, both two years (18% *v* 1·5%) and five years (34% *v* 3%) after operation (fig 1). The difference between the incidences of recurrent ulceration in these groups by life table analysis was highly significant ($p=0·001$; log rank test). There were no cases of recurrent ulceration among the patients who relapsed during maintenance treatment, which differed significantly from the outcome in the refractory group ($p<0·05$). Attendance for yearly follow up was invariably worse in the refractory group than in the group who healed with H_2 receptor antagonists.

Gastric secretion—Table II gives the basal and peak acid outputs in response to pentagastrin in the four groups and in patients with and without recurrent ulceration. Basal and peak acid outputs did not differ significantly among the four groups either before or after operation. Basal acid output, however, was higher ($p<0·05$) both before and after operation in the 14 patients who later suffered recurrent ulceration than in the 143 patients who did not have recurrent ulceration. Absolute differences, however, were small.

Insulin tests—Results of postoperative insulin tests (table III) were expressed both qualitatively (positive or negative) by Hollander's criteria[17] and Stempien's criterion[18] and in terms of the peak acid response to insulin minus basal acid output. Hollander early positive and late positive results were considered together; there were seven early positive results, 25 late

TABLE I—*Age, sex, and body weight of four groups of patients with duodenal ulcer classified according to response to H_2 receptor antagonists*

Group	No of patients	Men:women	Mean age in years (range)	Mean weight in kg (range)
Refractory ulcer	57	3·3:1	42·7 (19-66)	69·8 (41-103)
Relapse during maintenance treatment	19	2·6:1	43·0 (28-64)	69·7 (52-87)
Healed with H_2 receptor antagonists	67	2·2:1	44·3 (17-70)	68·9 (49-100)
No H_2 receptor antagonist	14	14·0:0	48·5 (27-68)	69·2 (60-80)

TABLE II—*Basal acid outputs and peak acid outputs in response to pentagastrin before and after highly selective vagotomy in the four subgroups of patients and in patients with and without recurrent ulceration. Values are medians (semi-interquartile ranges in parentheses)*

Group	Basal acid output (mmol/h)		Peak acid output (mmol/h)	
	Before operation	After operation	Before operation	After operation
Refractory ulcer	5·50 (3·22-9·63)	0·60 (0·10-1·20)	51·0 (38·8-59·5)	19·6 (13·8-26·9)
Relapse during maintenance treatment	4·45 (2·80-8·00)	0·20 (0·00-0·58)	50·0 (41·0-55·0)	17·6 (7·1-30·3)
Healed with H_2 receptor antagonists	6·15 (3·10-8·50)	0·35 (0·10-0·90)	45·0 (36·0-57·8)	17·1 (11·9-26·1)
No H_2 receptor antagonist	6·50 (2·45-10·73)	0·30 (0·00-0·85)	43·0 (33·0-50·0)	17·5 (11·7-25·4)
Patients with recurrent ulceration	8·65 (4·80-10·00) $p<0·05$	1·00 (0·40-1·30) $p<0·05$	51·5 (47·0-64·0)	23·3 (14·3-29·6)
Patients without recurrent ulceration	5·20 (3·00-9·10) $p<0·05$	0·40 (0·00-0·90) $p<0·05$	48·0 (37·0-57·8)	17·9 (12·0-26·0)

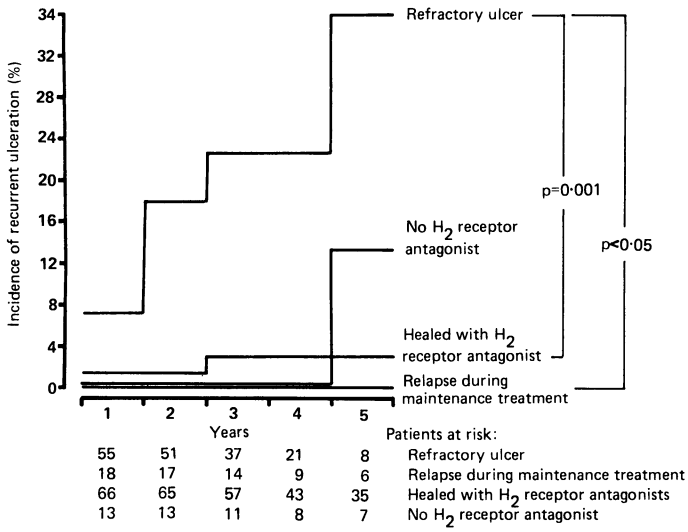

FIG 1—Cumulative incidences of recurrent ulceration after highly selective vagotomy in the four subgroups of patients.

positive results (23% positive results), and 109 negative results. Incidences of Hollander and Stempien positive test results were similar in the four groups of patients and also similar in patients with and without recurrent ulceration (table III). Peak acid outputs in response to insulin in patients who suffered recurrent ulceration after highly selective vagotomy were more than double those of patients who did not suffer recurrent ulceration (table III) but the mean difference was not significant.

Surgeons—Figure 2 gives the individual results for the four surgeons who performed most of the operations together with the results of 14 other surgeons, considered as a group, each of whom had performed only a few operations. There was considerable intersurgeon variation in the incidence of recurrent ulceration, the difference being significant between surgeons A and B ($p<0·05$). Recurrences tended to occur among patients in the refractory group, but even in these patients some surgeons achieved much better results than others. For example, after five years of follow up three of 13 patients in the refractory group operated on by surgeon A had suffered a recurrence compared with three of five patients operated on by surgeon B.

Cigarette smoking—Table IV shows the patients' smoking habits. Patients in the refractory group were the heaviest smokers, and patients who relapsed during maintenance treatment smoked more than those who remained healed with H_2 receptor antagonists. The difference between the refractory and healed groups was significant ($p<0·05$). Patients who suffered recurrent ulceration after vagotomy smoked almost twice as many cigarettes daily as patients who did not have a recurrence ($p<0·05$).

Discussion

In the post-cimetidine era the overall incidence of symptomatic recurrent ulceration after elective highly selective vagotomy for duodenal ulcer in this department was 6% at two years and 11% at five years (life table analysis). These incidences were higher than reported before the introduction of cimetidine.[11-13 19] Such historical comparisons are open to criticism because of the presence of uncontrolled variables such as changes in surgical staff and possibly changing patterns of referral. Nevertheless, we believe that since the introduction of H_2 receptor antagonists a less favourable group of patients with a more intractable ulcer diathesis is being referred for surgical treatment. The most striking feature of our results is the very high incidence of recurrent ulceration (34%) at five years among patients whose ulcers had failed to heal despite three months of H_2 receptor antagonist in full dosage. This incidence was significantly higher than among patients whose ulcers had healed with these drugs. Thus in contrast with patients with refractory ulcers, patients whose ulcers had healed with H_2 receptor antagonists, and indeed patients whose ulcers recurred during maintenance treatment, had favourable outcomes after highly selective vagotomy.

The proportion of patients available for follow up (76% at five years) was probably as high as could reasonably be achieved, given that the patient population was predominantly young to middle aged men, who are both mobile and disinclined to attend for follow up if they feel well. Nevertheless, there must be some doubt about

TABLE III—*Insulin test results judged by various criteria after highly selective vagotomy in the four groups of patients and in patients with and without recurrent ulceration*

Group	No of patients	No (%) Hollander positive	No (%) Stempien positive	Peak acid output in response to insulin* (mmol/h)		
				Median	Mean	Semi-interquartile range
Refractory ulcer	54	12 (22)	15 (28)	0·0	0·96	0-0·75
Relapse during maintenance treatment	18	5 (28)	6 (33)	0·0	0·91	0-0·80
Healed with H_2 receptor antagonists	56	13 (23)	10 (18)	0·0	0·86	0-1·20
No H_2 receptor antagonist	13	2 (15)	6 (46)	0·0	0·75	0-0·77
Patients with recurrent ulceration	14	3 (21)	4 (29)	0·1	1·73	0-1·05
Patients without recurrent ulceration	127	29 (23)	32 (25)	0·0	0·80	0-0·80

*Peak acid output minus basal acid output.

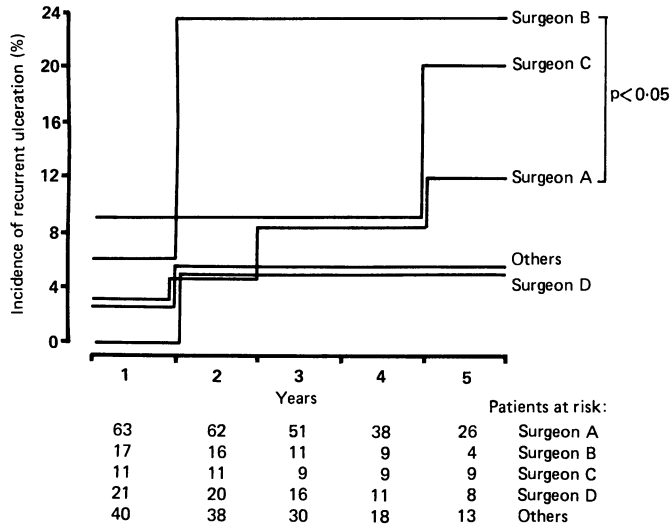

FIG 2—Cumulative incidences of recurrent ulceration after highly selective vagotomy performed by four individual surgeons and by a group of other surgeons, each of whom performed only a few procedures.

TABLE IV—*Smoking habits of various subgroups of patients*

Group	Smokers		Mean No of cigarettes/day	
	No	%		
Refractory ulcer	42	75	16·0	
Relapse during maintenance treatment	15	79	13·5	p<0·05
Healed with H_2 receptor antagonists	35	56	11·3	
No H_2 receptor antagonist	5	36	8·3	
Patients with recurrent ulceration	13	93	20·5	p<0·05
Patients without recurrent ulceration	76	55	11·5	
Patients in refractory group with recurrent ulceration	11	100	25·1	
Patients in refractory group without recurrent ulceration	32	73	16·3	

the accuracy of the results, as not all patients were treated. We find that patients with recurrent dyspepsia attend the clinic even if they have defaulted previously, so the incidence of recurrent ulceration may be less than calculated by the life table method. Nevertheless, even if all the patients in the refractory group who were not traced remained asymptomatic the incidence of recurrent ulceration in the refractory group would still be significantly higher than in the group who healed with H_2 receptor antagonists.

That patients whose ulcers fail to heal in response to H_2 receptor antagonists might also have a high incidence of recurrent ulceration after highly selective vagotomy has been considered before. Weaver and Temple, for example, found that highly selective vagotomy was effective treatment in patients who had been classed as failures with H_2 receptor antagonists, only one case of recurrent ulceration being found among 64 patients followed up for one to four years after operation.[20] By contrast, Hansen and Knigge reported that no fewer than 17 of 45 patients who had been classed as cimetidine failures suffered recurrent ulceration between 20 and 67 months after highly selective vagotomy.[21] Their study has been criticised, however, firstly, because a large number of surgeons were performing small numbers of highly selective vagotomies over a long period and, secondly, because no intraoperative or postoperative quality control was used, such as the Grassi[22] or insulin test.[23] In both studies patients had been referred because of "failure of H_2 receptor antagonists" but in neither study were they subdivided according to the precise nature of their preoperative responses to these drugs. In our study we found a precise definition of the preoperative response to H_2 receptor antagonists to be essential.

To try to define possible causes of failure of response, both to H_2 receptor antagonists and to surgical treatment, we examined such factors as the preoperative and postoperative basal and peak acid outputs, the results of the postoperative insulin test, the number of cigarettes smoked, and the surgeon who performed the operation. No correlation was found between the response to H_2 receptor antagonists and the preoperative and postoperative acid outputs. Basal acid output, however, was higher both before and after operation in patients who suffered recurrent ulceration after highly selective vagotomy than in patients who did not have recurrences; this has been noted before.[24] When the peak acid responses to pentagastrin in patients with recurrent ulceration were compared with those in patients without recurrence no significant differences were found either before or after operation.

The failure of the postoperative insulin test, as judged by several criteria, to predict recurrent ulceration after highly selective vagotomy was surprising, because we had previously found a correlation between Hollander positive insulin test results one week after operation and subsequent recurrent ulceration.[19] A possible explanation may be the small number of patients (14) who suffered recurrent ulceration in this series. An alternative explanation may be that the insulin test seeks to elicit an acid response and the magnitude of that response one week after operation may not be the principal determinant of recurrent ulceration in these patients with refractory ulceration.

In contrast with the weak influence of acid output on subsequent recurrent ulceration the effects of cigarette smoking, both on resistance to H_2 receptor antagonists and on recurrence after highly selective vagotomy, were more convincing. Patients with refractory ulcers smoked significantly more cigarettes daily than patients whose ulcers remained healed with these drugs, and patients who suffered recurrent ulceration after highly selective vagotomy smoked almost twice as many cigarettes as patients who did not have a recurrence. All the patients with refractory ulceration who suffered a recurrence smoked. Though there is no simple relation between smoking and acid output,[25-27] it has been shown that duodenal ulcers heal more slowly in smokers than non-smokers and that ulcer relapse rates after treatment is stopped are higher in smokers than non-smokers.[28] Resistance to H_2 receptor antagonists and recurrent ulceration after highly selective vagotomy may be related to decreased resistance of the gastroduodenal mucosa in patients who smoke, perhaps owing to impaired synthesis of prostaglandins.[29]

Recurrent ulceration after highly selective vagotomy is well recognised to be a surgeon related phenomenon,[6 9 10 19] and we found considerable intersurgeon variation in the incidences of recurrent ulceration at five years. Thus though most recurrences were found in the refractory group, some surgeons obtained better results in these patients than others. Hence patients with refractory ulcers appear to benefit from "better vagotomy," though gastric acid outputs one week after operation failed to identify these differences.

The question thus remains What is the best form of surgical treatment for refractory duodenal ulcers? Truncal or selective vagotomy combined with antrectomy, which has a low incidence of recurrent ulceration, might seem an attractive option. In most studies of vagotomy and antrectomy versus highly selective vagotomy, however, highly selective vagotomy has had superior overall results.[10 30 31] In a recent prospective randomised study the incidence of recurrent ulceration was not significantly lower after selective vagotomy and antrectomy than after highly selective vagotomy (2% *v* 6%).[10] It remains to be seen what the difference would be between these procedures when used in this resistant group of patients. The advantages of highly selective vagotomy, such as the virtual absence of diarrhoea, dumping, and bilious vomiting, which, if they occur, are so difficult to treat, and its low operative mortality, might still outweigh the potential advantages of more radical surgical procedures. We know, too, that most patients who suffer recurrent ulceration after highly selective vagotomy respond well to H_2 receptor antagonists,[32] even patients who had been refractory to these drugs before operation (unpublished data). In addition, the possibility of recurrence can be reduced by allowing the most experienced surgeon with the best clinical results to operate on these resistant, comparatively high risk patients. Such patients might also benefit from intraoperative testing of the completeness of vagotomy by the Grassi or Burge method[22 33]; recent evidence suggests that recurrence is unlikely in patients who have a negative Grassi test result, even if they had been refractory to H_2 receptor antagonists before operation.[34]

In conclusion duodenal ulcers that are refractory to H_2 receptor antagonists represent a more severe ulcer diathesis, in the treatment of which highly selective vagotomy is less effective. Though acid output before and soon after operation may affect the incidence of recurrent ulceration after highly selective vagotomy, its influence on outcome in the post-cimetidine era is relatively weak and other factors less amenable to measurement, such as mucosal resistance, may be more important.

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Surgical aspects of international drug smuggling

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Abstract

The internal concealment of cocaine and other drugs in packets by "body packers"—those who swallow packets of drugs or hide them in their vagina or rectum—to avoid detection by customs officials has been increasing in both the United States and Europe. The types of package and how they are concealed are changing as the traffickers become more sophisticated in their methods. The latest parcels are less likely to burst, but obstruction of the bowel may occur.

Awareness of the problem is important for staff of emergency medical services near international ports of arrival.

Introduction

Since the first report in 1975[1] reports of people smuggling drugs wrapped in packages and concealed either by swallowing or by insertion into the rectum or vagina have increased. Such people have been termed "body packers" or "mules" in America. In the United Kingdom they are referred to by staff of Her Majesty's Customs and Excise as "stuffers and swallowers." Early reports suggested a high mortality; many cases were diagnosed only at postmortem examination.[2] As the experience of the organisers of the smuggling has increased the packaging has become more sophisticated, and many survivors have now been reported.[3 4]

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Scale of the problem

The number of drug smugglers entering the United Kingdom has increased considerably over the past few years. The United Kingdom and Europe are now considered to be a growing market, as the American market is saturated with drugs and wholesale prices there are falling. Rates of detection have risen not only because of the growing numbers of smugglers but also because of more intelligence and better understanding of the habits of the organisers of the drug trade and methods used for concealing drugs. Sophisticated technology such as sniffer devices and kits of highly sensitive tests for confirming the presence of specific drugs in body fluids or on clothing plays a part in the detection of these crimes.

We analysed data supplied by HM Customs and Excise for September 1986. Of the 56 drug seizures at ports in the United Kingdom, 38 were of heroin (total 13·84 kg), 10 of cannabis (total 1288 kg), and eight of cocaine (total 4·15 kg). In 28 cases the drugs were concealed by swallowing or in the vagina or rectum. Thirty nine of the seizures were made at London Heathrow Airport and 11 at London Gatwick Airport. Other ports used during the month studied were Dover, Ramsgate, Folkestone, Plymouth, and the Scilly Isles. In other months Immingham, Liverpool, Bristol, Sheerness, and Glasgow have been used as ports of entry.

Interpol intelligence suggests that trafficking of cocaine is increasing considerably. In the first nine months of 1986 there were 47 seizures at European airports, amounting to 43 kg cocaine. Most of the 66 Colombians arrested after swallowing drugs were men aged 25-35. They were usually on their first trip to Europe, wearing a new suit and carrying a new Colombian or a forged Spanish or Portuguese passport. The maximum number of packets swallowed was 110; the total weight of cocaine ranged from 500 to 1290 g.

For every smuggler caught unknown numbers evade detection. In a recent exercise customs officers in Madrid made 800 passengers who had aroused their suspicion pass through an *x* ray machine. Radiological signs compatible with the presence of packets of cocaine in the gastrointestinal tract were seen in 160. We believe that few of these stuffers and swallowers appreciate the risk they take with their lives. Many are from poor backgrounds and are probably regarded by the organisers as expendable.

Interpol intelligence suggests that Colombian traffickers tend to concentrate on smaller European air and sea ports. At present 90% of all seizures of drugs in the United Kingdom take place at the two London airports. We suspect that these figures will change appreciably over the next year or so. Certainly, customs officers at all points of entry to the United Kingdom are now more vigilant. Thus more suspects will probably be taken to more hospitals with suspected perforation, with obstruction, or simply for radiological examination.

Ashford Hospital is close to London Heathrow Airport. We examine about six suspects a month radiologically to try to identify whether they have concealed drugs in their body. The customs officer in charge of the case obtains written permission from the subject before radiographs are taken.