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Address:
J.-F. Rey MD, General Secretary
Institut Arnault Tzanck
F-06700 St. Laurent du Var
France
Fax: +33-4 93-0 751 58
E-mail: jean-francois.rey@wanadoo.fr

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Flat Adenomas in the United Kingdom: Are Treatable Cancers Being Missed?

T. Fujii[1], B. J. Rembacken[2], M. F. Dixon[2], S. Yoshida[1], A. T. R. Axon[2]

[1] *National Cancer Centre East, Chiba, Japan*
[2] *Centre for Digestive Diseases, Leeds, United Kingdom*

Background and Study Aims: **The recognized pathway for colorectal malignancies is the adenoma-carcinoma sequence. It is estimated that up to two-thirds of colorectal carcinomas arise from adenomatous polyps. In recent years, Japanese workers have suggested that early colorectal malignancies may arise as "flat" or "depressed" rather than as polypoid lesions. Such flat or depressed adenomas and adenocarcinomas have not been widely recognized in the West. A prospective study was carried out to search for flat and depressed adenomas in a British population, using Japanese colonoscopic techniques.**

Patients and Methods: **In this prospective study at a British centre, 210 consecutive patients attending for routine colonoscopy were examined for flat or depressed lesions. The examinations were carried out using Japanese techniques by an experienced Japanese endoscopist (T.F.).**

Results: **Overall, 68 adenomas were found, of which 40 (59%) were polypoid, 26 (38%) were flat, and two (3%) appeared depressed. The majority of the adenomas contained areas of mild or moderate dysplasia, but four were severely dysplastic. Two of these were large polypoid tubulovillous adenomas, the third was a 7-mm protruding polyp, and the fourth was a depressed adenoma 6 mm in diameter. Three Dukes' stage A adenocarcinomas were also found. Of these, one was a 20-mm polyp, one a 15-mm flat elevation of the mucosa with a central depression, and the third a 6-mm depression of the mucosa. Finally, four Dukes' B or more advanced adenocarcinomas were found.**

Conclusions: **The polyp-carcinoma hypothesis prompts colonoscopists to search only for polypoid lesions when screening for malignancy. A significant proportion of early colorectal neoplasms may therefore be missed. European colonoscopists require training in the recognition of flat elevated and depressed lesions in order to detect colorectal malignancies in their early stages.**

Introduction

The hypothesis of the adenoma-carcinoma sequence suggests that colorectal cancers arise from adenomatous polyps (1–5), and this view has led to the belief that, if individuals undergo screening and the colon is cleared of premalignant polyps, the risk of colorectal cancer can be reduced, if not eliminated altogether (6, 7). Morson estimated that up to two-thirds of colorectal carcinomas arise from adenomatous polyps. He was unable to explain the origin of the remainder (8).

A possible explanation for the remaining one-third of carcinomas has been advanced by Japanese workers. They suggest that some early colorectal malignancies arise as "flat" or "depressed" rather than as polypoid lesions (9–15). Flat or depressed adenomas and carcinomas are commonly described in the Japanese literature. Although there is a higher incidence of colonic malignancy in Europe and the United States than in Japan, flat or depressed lesions have not been widely recognized. These lesions may have important implications for cancer prevention programmes, since colonoscopic screening will be of limited value if it fails to detect them.

A prospective study was therefore undertaken to determine whether flat or depressed neoplasms can be detected by colonoscopic examination at one centre in the United Kingdom.

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Methods

Two hundred and ten consecutive patients attending for routine colonoscopy were screened for flat or depressed neoplasms. Informed consent was obtained from all patients. Two patients with familial adenomatous polyposis were excluded. The patients' average age was 58 years, with a male : female ratio of 7 : 10. The bowel preparation included 2–5 l of Klean-Prep on the day of an afternoon examination or on the evening before in patients who were to undergo the examination in the morning.

All examinations were carried out by the same operator (TF), using an Olympus CF-200 Z magnifying colonoscope and alternatively a standard Olympus 200 I colonoscope. A magnifying colonoscope, together with dye spraying, allows close examination of the mucosal crypt pattern of suspicious lesions. Metaplastic polyps, mild or moderately dysplastic adenomas, severely dysplastic adenomas, and Dukes' stage A carcinomas can be distinguished using this technique. Without the magnifying colonoscope, metaplastic polyps may be removed unnecessarily, and some early carcinomas may be inappropriately treated with endoscopic mucosal resection when surgical resection would have been preferable.

Ninety per cent of the 189 examinations were completed to the caecum. The examination was abandoned due to poor bowel preparation in 11 cases, severe sigmoid diverticular disease in eight cases, and persistent looping of the endoscope in two cases. Patients were sedated with midazolam at a mean dose of 4 mg. In addition, hyoscine butylbromide (Buscopan) 20 mg was administered intravenously in patients in whom there was no contraindication to its use. The clinical indications for all examinations are listed in Table **1**. Suspicious lesions were sprayed with indigo carmine dye (0.2%) to help identify their size and shape. The dye was injected directly into the biopsy channel, using a 20-ml disposable syringe.

The diagnosis of dysplasia and adenocarcinoma was made according to the World Health Organization system (16). According to this classification, severe dysplasia is characterized by marked loss of nuclear polarity and irregular glandular architecture, but not breaching the muscularis mucosa. The malignant lesions were classified as "early adenocarcinomas" when the malignant cells infiltrated the submucosa but did not involve the muscularis propria.

Japanese classification. The Japanese Research Society for Cancer of Colon and Rectum has recommended a system for the macroscopic classification of early colorectal carcinomas (17). Lesions are described as protruding, flat elevated, flat and depressed. The depressed cancers were later divided into two subgroups by Kudo (18). This classification, detailed in Table **2**, was used in the study.

Treatment of polyps. All flat or sessile lesions less than 20 mm in diameter were completely removed by endoscopic mucosal resection (EMR) as described by Kudo and others (19–22). Since depressed lesions larger than 10 mm in diameter have a high incidence of invasive malignancy, the maximum depressed lesion we would remove by EMR is 10 mm in diameter (18). The technique of EMR is briefly as follows: a needle is inserted alongside the lesion, and 2–5 ml of saline is injected to lift it above the surrounding mucosa. Once the lesion has been raised, a snare containing four sharp spikes is applied over the lesion and closed. The snare is then relaxed slightly to allow the submucosa to retract, minimizing the risk of perforation. The lesion is removed using blend or cutting current, and the lesion is grasped with a five-pronged grasping forceps.

Pedunculated polyps were removed by snare polypectomy, and lesions suspicious of more advanced malignancy (Dukes' stage B or higher) were biopsied. Polyps smaller than 5 mm were treated by hot biopsy. A detachable snare was usually applied before cutting thick-stalked polyps, to minimize bleeding (23). Specimens resected by EMR were pinned out and fixed in 10% formalin for 24–48 hours. The fixed specimens were then surface-stained with haematoxylin for 30 seconds, photographed by stereo microscope, and then examined histologically.

Table 1: Indications for colonoscopy.

Presenting complaint	n	Prevalence (%)
Change in bowel habit	45	22
Polyp surveillance	47	23
Surveillance for ulcerative colitis	31	15
Rectal bleeding	24	11
Anaemia	16	8
Abdominal pain	4	2
Other	18	9
Postsurgical cancer surveillance	23	10
Total	208	100

Table 2: Japanese classification of colorectal lesions.

	Japanese classification	Macroscopic appearance
Protruding lesions	Ip	Pedunculated polyps
	Ips	Subpedunculated polyps
	Is	Sessile polyps
Flat elevated lesions	IIa	Flat elevation of mucosa
	IIa + IIc	Flat elevation with central depression
Flat lesions	IIb	Flat mucosal change
Depressed lesions	IIc	Mucosal depression
	IIc + IIa	Mucosal depression with raised edge

Results

Sixty-eight adenomas were found in 47 of the 208 patients (22%) in the study. Eight flat hyperplastic polyps were also removed by EMR. Of the 68 true adenomas, 40 (59%) were polypoid, 26 (38%) were flat, and two (3%) appeared depressed. There was no difference in the clinical indications for colonoscopy in patients with polypoid and flat lesions. Although 31 examinations were carried out as part of our ulcerative colitis surveillance program, only one sessile adenoma was found in this group.

Most patients had only one adenoma, but 14 had two adenomas, and two patients had three. Twenty small adenomas (12 sessile and six flat) were treated by hot biopsy, 25 pedunculated adenomas were removed by snare polypectomy, and 23 flat adenomas were removed by endoscopic mucosal resection.

The majority of the adenomas contained areas of moderate dysplasia, but four showed severe dysplasia (5.8%). The four patients (three women and one man) with severely dysplastic adenomas were aged between 41 and 79, with a mean age of 66. The reasons for colonoscopy in these four patients were: previous colorectal cancer (one patient), change of bowel habit (one patient) and previous polyps (two patients). Two of the severely dysplastic adenomas were large polypoid tubulovillous adenomas, and one was a 7-mm polyp. The last severely dysplastic lesion was a 6-mm depression of the mucosa (Figure **1 a–d**). There were no cases of intramucosal carcinoma alone.

Three Dukes' A adenocarcinomas were also found (4.4%). The three patients concerned were all men, aged 55, 71, and 71 years, undergoing colonoscopy for a family history of colorectal carcinoma, a previous colorectal carcinoma, and previous colorectal polyps, respectively. One of the Dukes' A carcinomas was polypoid, one was a flat elevation of the mucosa with a central depression, and the third was a 15-mm depression of the mucosa (Figure **2 a–d**). The characteristics of the severely dysplastic and carcinomatous lesions are detailed in Table **3**. Four Dukes' stage B or more advanced carcinomas were also found.

The only complication was a case of brisk bleeding after snare polypectomy of a thickly stalked pedunculated polyp.

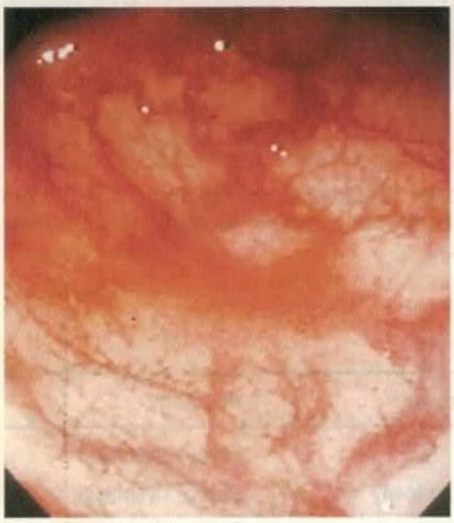

Figure 1 a: Colonoscopy, showing a 6-mm erythematous patch in the rectum of a 79-year-old British woman.

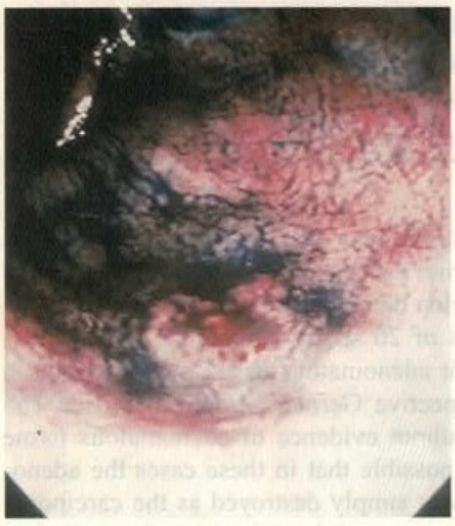

Figure 1 b: After indigo carmine dye spraying, the lesion appeared depressed, with a slightly elevated margin.

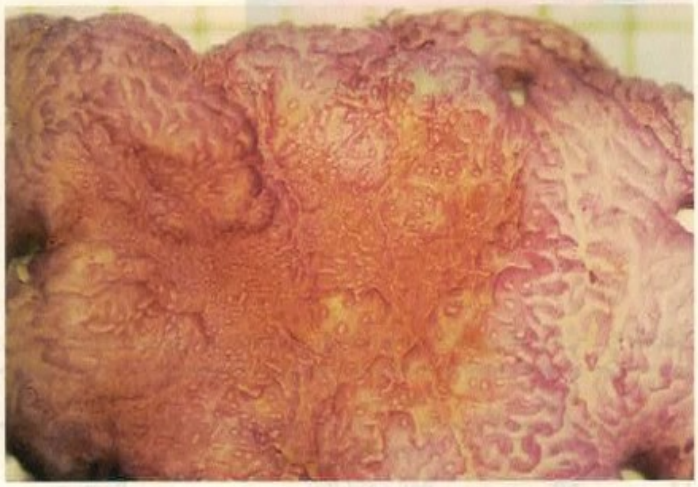

Figure 1 c: On stereo microscopy, the crypt pattern was found to be distorted.

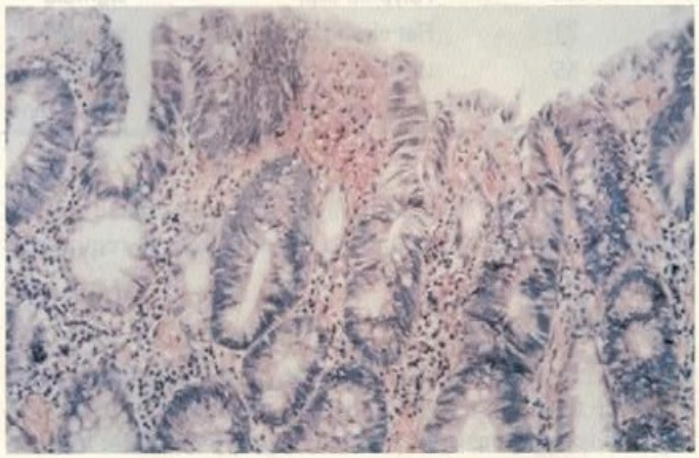

Figure 1 d: The histology confirmed a tubular adenoma with focally severe dysplasia.

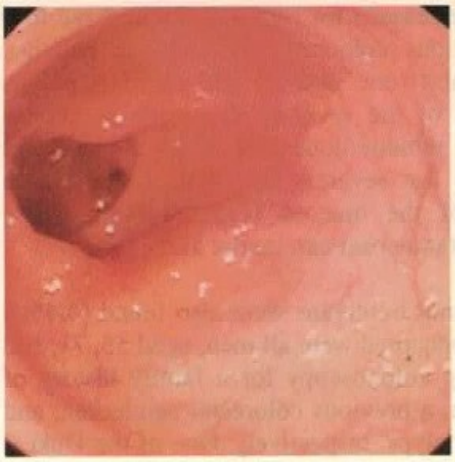

Figure 2a: This 12-mm erythematous patch was found at the splenic flexure in an asymptomatic 71-year-old British man undergoing colonoscopy due to a family history of colorectal carcinoma.

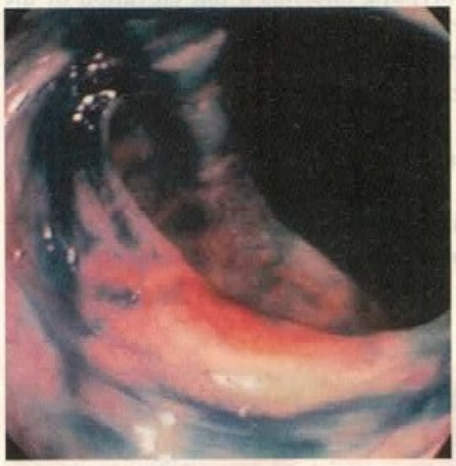

Figure 2b: After indigo carmine dye spraying, the lesion appeared depressed.

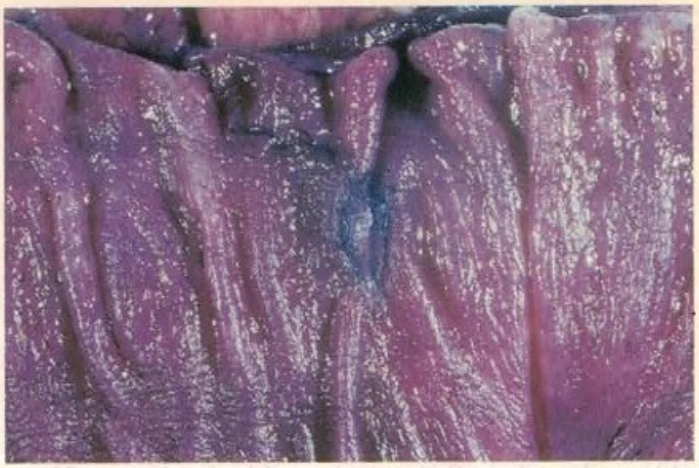

Figure 2c: The stereo-microscopic image of the resected lesion shows that the mucosal crypts have been completely destroyed.

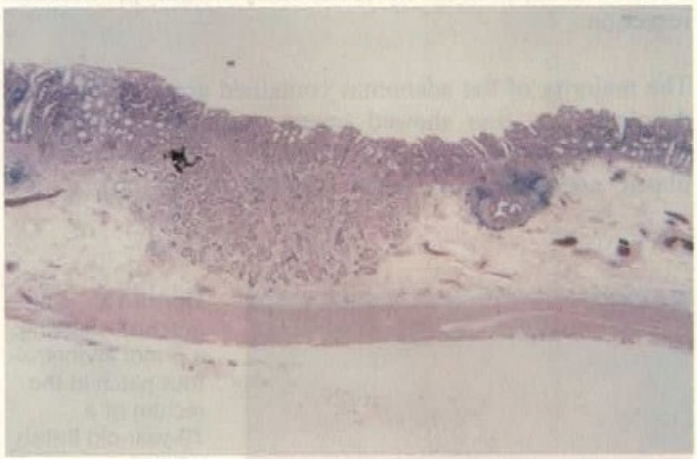

Figure 2d: A low-power histological view of the cut section in the resected specimen confirmed a Dukes' A carcinoma with invasion into the submucosa.

Table 3: Characteristics of the four severely dysplastic adenomas and three Dukes' A carcinomas.

Sex	Age	Lesion	Site	Size (mm)	Removal	Histology
F	79	Depressed (IIc)	Rectum	6	EMR	Severe dysplasia
M	68	Polypoid (Ip)	Rectum	20	Polypectomy	Severe dysplasia
F	77	Polypoid (Isp)	Sigmoid	14	Polypectomy	Severe dysplasia
F	41	Polypoid (Isp)	Sigmoid	7	Polypectomy	Severe dysplasia
M	71	Flat elevated (IIa + IIc)	Sigmoid	15	Surgical resection	Dukes' A carcinoma
M	55	Ulcerated polyp	Sigmoid	20	Surgical resection	Dukes' A carcinoma
M	71	Depressed (IIc)	Descending	15	Surgical resection	Dukes' A carcinoma

The bleeding was stopped by applying three metal clips to the mucosal defect (24), and no transfusion was required.

Discussion

Morson proposed the adenoma-carcinoma sequence to explain the development of colorectal carcinoma (1). According to this hypothesis, adenomatous polyps become increasingly dysplastic as they enlarge and eventually progress to adenocarcinoma. Morson suggested that up to two thirds of colorectal carcinomas may develop in this way (3). It has been suggested that the remaining one-third of colorectal cancers may develop de novo from normal mucosa (25–32). Indeed, a series of 20 small carcinomas without evidence of concomitant adenomatous tissue was described in 1962 (33). A retrospective German review identified 155 small carcinomas without evidence of adenomatous tissue (34). However, it is possible that in these cases the adenomatous component was simply destroyed as the carcinoma grew. Bedenne et al. proposed the existence of two distinct

types of colorectal cancers: an exophytic type, accounting for about 60% of cases and arising from the adenoma-carcinoma sequence; and an ulcero-infiltrating type, accounting for 40% and developing de novo (35).

An alternative explanation for the origin of the other one-third of colorectal carcinomas is that they arise as "flat" or "depressed" rather than as polypoid lesions (36,37). These flat or depressed adenomas and adenocarcinomas are commonly reported in the Japanese literature. According to retrospective reviews in Japan, 12–40% of adenomas and early colorectal carcinomas are flat rather than polypoid (38,39). In the German study mentioned above, the majority of early carcinomas were polypoid, but one-third appeared as flat elevations of the mucosa (59% vs. 34%). Outside Japan, there have also been reports of small, flat neoplastic lesions (40–45). Lanspa et al. concluded that flat adenomas have the same prevalence as other adenomas, and suggested that this type may represent an early stage of adenoma formation (46). Lynch et al. reported on the clinical and pathological features of four extended kindreds with the hereditary flat adenoma syndrome, and suggested that this is a variant of familial adenomatous polyposis (47).

There is some evidence to suggest that flat elevated lesions have a higher malignant potential than the polypoid type. Studies by Muto et al. have shown a much higher frequency of aneuploidy in flat elevated adenomas compared to the polypoid type (48). Wolber and Owen reported that small flat adenomas were ten times more likely to contain high-grade dysplasia than polypoid adenomas (49). Rubio et al. (50) recently contrasted the histological findings in 90 flat neoplasias found in Sweden with 141 flat neoplasias resected in Tokyo. In their series, 24.8% of the Japanese flat adenomas contained severe dysplasia, compared with 13.3% of the Swedish lesions.

Data from the present study suggest that the risk of malignancy in flat elevated adenomas is less than this. Of the 26 flat elevated lesions detected, 25 (96%) were only moderately dysplastic and only one lesion, containing a central depression, was a Dukes' A carcinoma. In contrast, four of the 40 polypoid lesions (10%) were either severely dysplastic (three lesions) or invasive (one Dukes' A carcinoma). These data also highlight the aggressive nature of depressed lesions. Only two depressed lesions were found – one severely dysplastic and the other a Dukes' A carcinoma. Kudo et al. have also drawn attention to the high incidence of severe dysplasia in small depressed lesions (6–10 mm) compared with flat elevated neoplasia (50% vs. 2.4%) (18).

Jaramillo et al. looked for flat adenomas, using Japanese techniques, in 85 patients with chronic ulcerative colitis (51). They found 23 flat adenomas – 21 with low-grade dysplasia and two with high-grade dysplasia. It is almost impossible to distinguish mild dysplasia from the simple mucosal inflammation in ulcerative colitis (52,53). The group at St Mark's Hospital, London, re-analysed their data, applying stricter histological criteria for diagnosing low-grade dysplasia (54). Excluding Dukes' A lesions, they only accepted nine patients as having low-grade dysplasia out of the 51 diagnosed earlier. In addition, the histopathologists agreed on a diagnosis of low-grade dysplasia in less than half the cases.

Depressed lesions may be difficult to find at colonoscopy, and those identified in the present series only appeared as faint patches of mucosal hyperaemia. To recognize flat and depressed lesions, bowel preparation must be optimal and the colonoscopist must have received training in recognizing such lesions.

Although this prospective study involved a relatively small number of patients, it was nevertheless possible to confirm the presence of both flat and depressed adenomas, as reported in Japan. Japanese reviews have indicated that the depressed type of adenoma is rare (18,38,55). In this prospective study, we found two such lesions, one with early adenocarcinoma and the other containing severely dysplastic epithelium.

Conclusions

The recognition that colorectal malignancies may appear flat or depressed has important implications. The polyp-cancer hypothesis only prompts colonoscopists to search for polypoid lesions when screening for malignancy, and a significant proportion of early colorectal neoplasms may therefore be missed. Evidence from the two largest studies suggests that this is indeed the case. The National Polyp Study in the United States reported on the six-year follow-up of 1418 patients after repeated colonoscopies to clear all polyps (56). This study did not incorporate a control arm, but if the background age-specific and sex-specific incidence of colorectal cancer is used as a control group, removal of all polyps failed to prevent up to 24% of all subsequent carcinomas. The National Polyp Study does not elaborate on the detailed appearances of the five carcinomas that were missed, other than providing data on their sizes (6 mm, 8 mm, 15 mm, 15 mm, and 25 mm). It is noteworthy that the cancers were unusually small, suggesting an aggressive growth pattern. The larger Veterans' Affairs study of 32702 patients found that endoscopy only prevented 50% of all subsequent colorectal cancers (57). Some patients had, however, only been examined with the flexible sigmoidoscope.

In the present study, three of seven malignant or premalignant lesions would have gone undetected if screening for flat and depressed as well as polypoid lesions had not been carried out. European colonoscopists require training in the recognition of flat elevated and depressed lesions in order to detect colorectal malignancies in their early stages.

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Corresponding Author

B. Rembacken, M.D.
Centre for Digestive Diseases
The General Infirmary at Leeds
Great George Street
Leeds LS13EX
United Kingdom
Fax: +44-113-226-1463
E-mail: BJR@thecafe.co.uk

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Congress Announcements

Argentina

April 17, 1998	**S.A.G.E. – F.A.G.E. – A.A.E.D. Meeting** Hospital General San Martín de La Plata	*Information:* Dirección Postal: Luis do Tejeda, 4337 5009 Cerro de la Rosa, Córdoba, Pcia. de Córdoba, República Argentina Tel./Fax: 0054-51 81 0994
June 25–26, 1998	**II. Course of Therapeutic Endoscopy** **Tucuman Digestive Endoscopy Association** Sheraton Hotel, Buenos Aires	*Information:* Dr. Bernard Babot Fax: 0054-81 32 2858 Dr. Jorge Romaña Murga Tel. 0054-81 22 3803
July 31, 1998	**F.A.G.E. – A.A.E.D. Course 1998** Córdoba	*Information:* Dirección Postal: Luis do Tejeda, 4337 5009 Cerro de la Rosa, Córdoba, Pcia. de Córdoba, República Argentina Tel./Fax: 0054-51 81-0994
December 6–10, 1998	**Argentine Congress of Gastroenterology and Digestive Endoscopy 1998** Sheraton Hotel, Buenos Aires	*Information:* MCI Congresos Viamonte 969 6° "A" Capital Federal Argentina Tel. 0054-1 325 1290 Fax: 0054-1 325 1273