

# Tissue staining (chromoscopy) of the gastrointestinal tract

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**MB Fennerty. Tissue staining (chromoscopy) of the gastrointestinal tract. Can J Gastroenterol 1999;13(5):423-429.** Tissue staining, or chromoscopy, is used as an adjunctive technique during gastrointestinal endoscopy. Chemical agents are applied to the gastrointestinal mucosal surface to identify specific epithelia or to enhance the mucosal surface characteristics of the gastrointestinal epithelium. This aids in the recognition of subtle lesions (ie, polyps) or allows directed targeting of biopsies (ie, sprue or Barrett's esophagus) to increase the yield of endoscopic diagnostic accuracy. The four endoscopic tissue-staining techniques in use are vital staining, contrast staining (chromoscopy), reactive staining and tattooing. Some of the agents used for endoscopic tissue staining and the uses of chromoscopy in identifying pathology of the esophagus, stomach, small bowel and colon during endoscopy are discussed.

**Key Words:** *Chromoscopy; Endoscopy; Tissue staining*

## Coloration tissulaire (chromoscopie) des voies digestives

**RÉSUMÉ :** La coloration tissulaire, ou chromoscopie, est utilisée comme technique d'appoint durant l'endoscopie gastro-intestinale. Des agents chimiques sont appliqués à la muqueuse gastro-intestinale pour identifier les épithélia spécifiques ou pour rehausser les caractéristiques de surface de la muqueuse de l'épithélium gastro-intestinal. Cette technique facilite la reconnaissance des lésions discrètes (par exemple, polypes) ou permet un ciblage plus direct des biopsies (par exemple, sprue ou œsophage de Barrett) afin d'augmenter la précision diagnostique de l'endoscopie. Les quatre techniques de coloration tissulaire endoscopique en usage sont la coloration vitale, la coloration de contraste (chromoscopie), la coloration réactive et le tatouage. On présente ici certains des agents utilisés pour la coloration tissulaire endoscopique et les emplois de la chromoscopie pour l'identification des pathologies de l'œsophage, de l'estomac, du grêle et du côlon durant l'endoscopie.

Tissue staining, or chromoscopy, is an adjunctive endoscopic technique using chemical agents applied to the gastrointestinal mucosal surface to identify specific epithelia or to enhance the mucosal surface characteristics of the gastrointestinal epithelium. Chromoscopy is performed to aid in the recognition of subtle lesions (ie, polyps), or to allow directed targeting of biopsies (ie, sprue or Barrett's esophagus) to increase the yield of endoscopic diagnostic accuracy.

There are four endoscopic tissue staining techniques: vital staining, contrast staining (chromoscopy), reactive staining and tattooing (1-4). Vital staining is the use of an agent that is absorbed by the gastrointestinal epithelium, allowing the identification of a characteristic epithelium. An example of vital staining is the use of methylene blue to identify gastric intestinal metaplasia. Contrast staining, or chromoscopy, is the use of an agent to accentuate the surface topography of the gastrointestinal mucosa, allowing the identifica-

tion of subtle changes that otherwise may be unrecognized. An example of chromoscopy is the use of indigo carmine to identify flat colonic lesions. The term 'chromoscopy' is used interchangeably with 'tissue staining' to refer to all forms of these tissue staining techniques. Reactive staining is the use of agents that identify chemical reactions within the gastrointestinal tract. For instance, Congo red turns black in the presence of acid and has been used to identify acid-secreting portions of the stomach. Tattooing is a technique that uses either short-acting or permanent agents such as India ink to mark a specific mucosal site for longitudinal study.

Chromoscopy is not a new technique. Tissue staining was performed by pathologists for many years before the development of the endoscope (4). These techniques were adapted to endoscopic practice shortly after the introduction of rigid and fiberoptic instruments. Tissue stains are usually 'sprayed' onto the mucosal surface during endoscopy, but have also

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**TABLE 1**  
**Tissue stains**

Class	Use
Tattooing agents	
India ink	For permanent marking of a mucosal site for relocalization at the time of surgery or endoscopy. Used in the esophagus, stomach and colon. Safe and without side effects.
Indocyanine green	Shorter-duration tattooing agent than India ink.
Absorptive stains	
Lugol's iodine	Stains normal glycogen-containing squamous mucosa in the esophagus, allowing recognition of abnormal squamous epithelium (dysplasia) or metaplastic epithelium (Barrett's esophagus).
Methylene blue and toluidine blue	Stains the absorptive epithelium (small bowel and colon), allowing the identification of metaplastic epithelium in the esophagus (Barrett's esophagus) and stomach (gastric intestinal metaplasia). Also can identify gastric metaplasia (negative stain) in the duodenal bulb.
Contrast stains	
Indigo carmine and cresyl violet	Accentuates mucosal topography, allowing recognition of abnormal small bowel (sprue) and colonic mucosa (inflammatory bowel disease, polyps).
Reactive stains	
Congo red	Identifies acid-secreting portions of the stomach postoperatively; documents achlorhydria.
Phenol red	Identifies alkaline areas of the stomach.

been given orally and rectally before the procedure. Despite chromoscopy's many uses and advantages, this endoscopic technique is not often used by North American endoscopists, and few endoscopists have been formally trained in chromoscopy (2).

Some of the agents used for endoscopic tissue staining and the uses of chromoscopy in identifying pathology of the esophagus, stomach, small bowel and colon during endoscopy are discussed.

### TISSUE STAINING

Many different chemical compounds have been used as tissue staining agents (Table 1). Vital or absorptive stains include Lugol's solution, indocyanine green (IG), methylene blue and toluidine blue. Lugol's solution is an inexpensive, widely available, nontoxic mixture of iodine and potassium iodide forming a compound iodine solution. First described by the Parisian Jean Guillaume Auguste Lugol in the 1800s, Lugol's solution stains the normal nonkeratinized squamous epithelium of the normal esophagus. Lugol's solution is taken up by squamous epithelium because of glycogen's affinity for iodinated agents. Once absorbed by the squamous

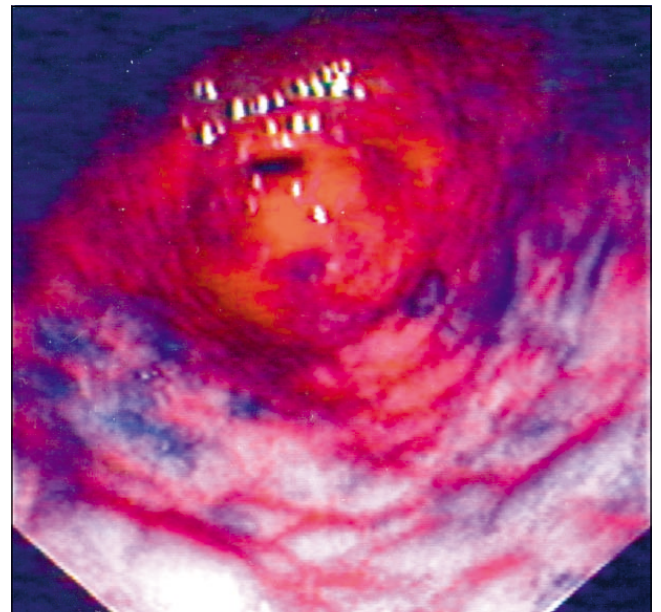
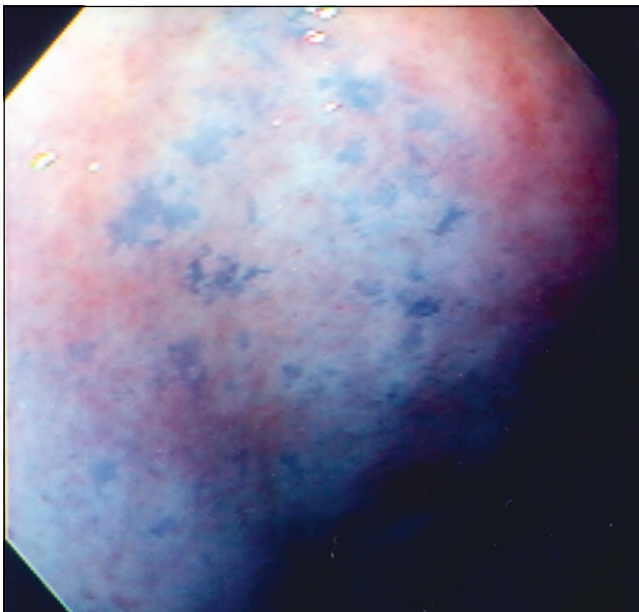
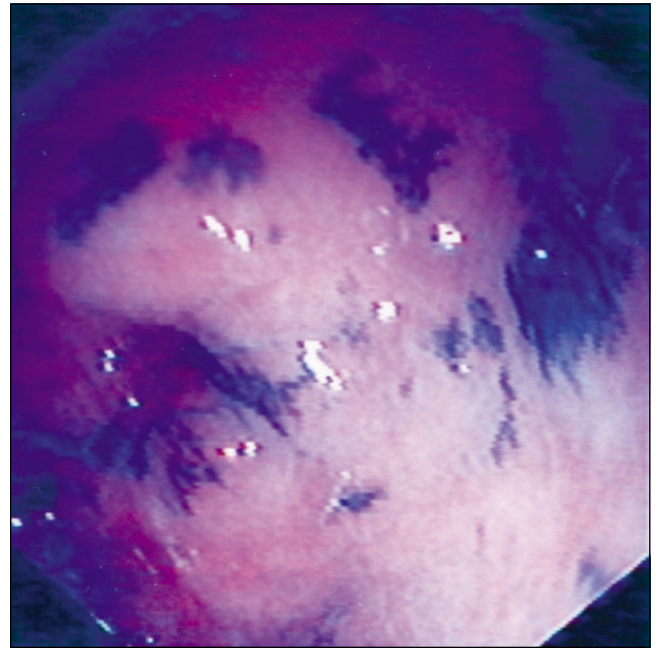
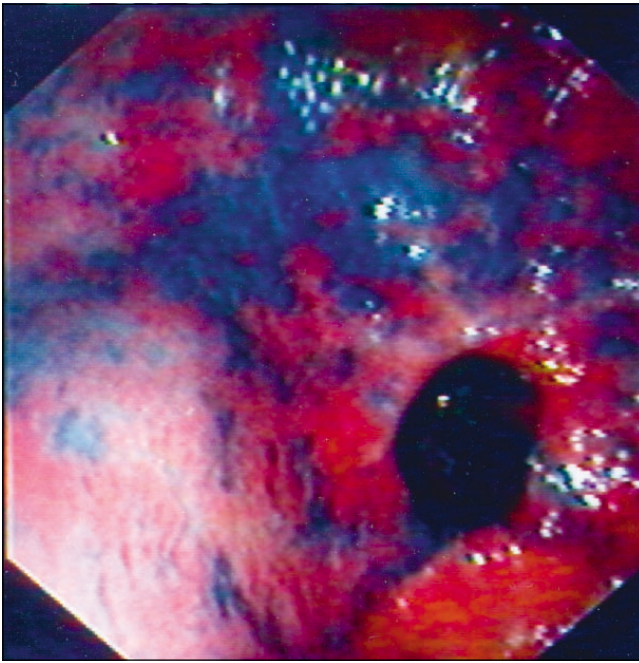
epithelium, Lugol's solution results in a characteristic green-brown colour, the intensity of which is in part dependent upon the amount of glycogen present. The absence of staining with Lugol's solution can be used to identify abnormal epithelium such as inflammatory squamous epithelium, neoplastic squamous epithelium or metaplastic epithelium within the esophagus. Lugol's solution appears to be safe, although in one study a patient later found to be allergic to iodine developed bronchial spasm following its use in the esophagus (5). Lugol's solution should, therefore, be used cautiously in patients with reported iodine sensitivity. In the same study, three of 46 individuals also reported transient heartburn following installation of a 50% solution into the esophagus (5).

IG is composed of 1 to 2  $\mu\text{m}$  dimers and polymers of a carbon, nitrogen and sulphur compound in solution. IG (5 mg/kg) is usually given as an infusion of 5% albumin 15 to 30 mins before visualization of the liver. Following infusion, IG is taken up by normally functioning hepatocytes, allowing one to differentiate normal from abnormal hepatocellular function. Thus, IG enhances the identification of diseased hepatic tissue for directed biopsy during open or laparoscopic visualization of the liver. IG has also been used as a colonic tattooing agent, but is less widely studied than the more commonly used and widely available endoscopic tattoo, India ink.

Methylene blue (methylthionine chloride) is a nontoxic carbon-based chemical agent that reversibly stains actively absorbing epithelium such as the epithelium of the small intestine and colon. Methylene blue is not absorbed by the squamous epithelium of the esophagus or the columnar epithelium of the stomach. However, metaplastic epithelium with absorptive characteristics such as intestinal metaplasia in the stomach (gastric intestinal metaplasia) or esophagus (Barrett's esophagus) is capable of absorbing the stain. Methylene blue can be used to identify this metaplastic absorptive epithelium or gastric metaplasia of the duodenal bulb in the absence of uptake when used in the small intestine (6,7).

Following application of 10 to 50  $\text{cm}^3$  of a 5% to 10% solution of methylene blue either orally preprocedure or during endoscopy by spraying, uptake of the stain occurs within 2 to 3 mins, which is then resistant to vigorous washing or lavage (Figure 1). The stain fades over the next 15 to 30 mins but persists, in most patients, for up to 12 to 24 h until the stain is lost, secondary to renal excretion or cellular loss. The stain is preserved in frozen section biopsy specimens but lost during permanent tissue fixation with formalin and alcohol. Methylene blue results in blue discoloration of the urine and stools for the next 24 to 48 h.

In order for methylene blue to come into contact with absorptive epithelium and allow staining, surface mucus must first be removed. Proteinase (pronase) and mucolytic agents (*N*-acetylcysteine [Mucomyst, Bristol Laboratories, Evansville, Indiana]) have been used to remove the mucous layer. *N*-acetylcysteine contains sulphhydryl groups that result in the disruption of disulphide bridges of the mucous layer. This



**Figure 1)** Prominent focal (Top left, top right, bottom left) and subtle diffuse (Bottom right) staining, following application of 10% N-acetylcysteine and a 5% solution of methylene blue

action destroys the glycoproteins critical to the integrity of the mucous cap, resulting in disintegration of the mucous layer. N-acetylcysteine can be given orally or sprayed directly onto the mucosal surface before application of methylene blue. However, N-acetylcysteine has a foul taste and a sulphurous odor, making oral ingestion unpleasant, and this form of application is rarely used.

Toluidine blue stains neoplastic cell nuclei. This basic metachromatic dye has been postulated to either have a tropism for the rapidly proliferating cells, characteristic of neoplastic tissue, or stain related to its absorption based on decreased cellular adhesion and ability to penetrate what

was previously a 'tight junction'. Toluidine blue's most common application, as a tissue stain, has been in the identification of neoplastic oral squamous epithelium when used as a 1% solution, following a 1% application of acetic acid to remove surface debris. No toxicity or side effects have been observed with this agent when used for this purpose.

#### CONTRAST STAINS (CHROMOSCOPY)

Contrast stains (chromoscopy) include cresyl violet and indigo carmine. Cresyl violet pools in the margins of the colonic pits, resulting in a 'stain', highlighting the topography of the colonic epithelium. While less commonly used during



**Figure 2)** Esophageal India ink tattoo used before studying the thermal ablation of Barrett's esophagus

chromoscopy than indigo carmine, it appears to be an effective, nontoxic agent when used as a colonic contrast stain.

Indigo carmine is a blue nontoxic dye (indigo) derived from plants combined with carmine, a compound of cochineal and alum, which forms a red colouring agent. Indigo carmine is not absorbed and percolates across the surface of the epithelium following application. The stain collects in the sulci and grooves of the mucosa, highlighting the topography of the stained epithelium. Indigo carmine has been given as 100 mg of a powder in a capsule, or sprayed onto the mucosa as a 0.1% to 2% solution. No side effects or toxicity of indigo carmine has been described.

### REACTIVE STAINING

Reactive staining is the use of pH-dependent dyes that can be used to highlight acid-secreting or alkaline-associated epithelia. Congo red, in the presence of acid (pH less than 3), decomposes, resulting in a colour change from red to a blue-black pigment. Congo red is almost always used with a secretagogue such as pentagastrin to detect acid-secreting epithelium. Pentagastrin is used to insure adequate acid secretion to enhance the accuracy of the test. Pentagastrin (250 mg) is usually given intramuscularly 30 mins before the procedure, and then surface acid is neutralized with a 0.5% sodium hydroxide solution before spraying 10 to 50 cm<sup>3</sup> of Congo red in a 0.3% to 0.5% solution directly onto the surface epithelium in the stomach or duodenum. Congo red is nontoxic and without side effects.

Phenol red is a yellow agent that turns red in the presence of alkali. This agent has been used to depict areas with high *Helicobacter pylori* concentration, as well as atrophic gastritis. Phenol red, as is the case with Congo red, appears to be nontoxic and without side effects.

### TATTOOING AGENTS

India ink has been the most widely used tattooing agent. India ink is a colloidal suspension of carbon particles. The carbon is derived from incomplete combustion of petroleum products in an oxygen-depleted system. When this carbon powder is combined with dilutants, stabilizers and surfactants such as alcohol, shellac, phenol and ammonia, India ink is formed. While there are numerous manufacturers of this product, all of the products contain the amorphous carbon particles characteristic of India ink.

Carbon tattooing has been used for decades to tattoo the skin without toxicity, and India ink tattoos of the gastrointestinal tract appear similarly to be safe. Tattooing of the colon with a black tattoo dye was first attempted by Knoerchild in 1962 (8), using a rheostat inserted through a rigid proctoscope. Tattooing via an injection catheter at the time of flexible endoscopy was described in 1975 (9). Since then, more than 200 cases of tattooing of the esophagus, stomach and colon have been described in the literature (10-12). The tattoo obtained with this technique appears to be long lasting, if not permanent. Although 'histological' complications of fat necrosis, inflammation, abscess and focal peritonitis have been described, they have not resulted in any clinical sequelae, and these pathological 'complications' were only serendipitous findings. Furthermore, long term safety appears to be a nonissue because there is little or no inflammatory response to the amorphous carbon particles remaining in the lamina propria and submucosa (10-12).

India ink, diluted in a one to 10 ratio with sterile saline, can be prepared in a 5 mL high pressure liquid chromatography vial and then autoclaved. Alternatively, the solution can be drawn through a millipore filter needle. The latter technique removes a substantial portion of the carbon, which may affect the quality and persistence of the stain. Tattoos with India ink are usually applied by injecting less than 1 mL of the sterilized solution with a sclerotherapy needle. After the sclerotherapy needle is purged with 0.75 to 1.25 mL of India ink, a 0.3 to 0.5 mL aliquot of solution is injected tangentially to provide a small bleb in the mucosa (Figures 2,3). Care should be taken to avoid deep injection, which stains the peritoneum and may obscure the surgeon's view, or luminal spillage, which makes further endoscopic inspection somewhat difficult.

Methylene blue, indigo carmine and toluidine blue have also been used as tattooing agents with little success, related to their transient staining qualities. However, IG appears to be longer lasting, although it does not result in a persistent stain, limiting its applicability as a tattooing agent.

### TISSUE STAINING OF THE ESOPHAGUS

**Squamous epithelium:** In the esophagus, Lugol's solution of potassium iodine can be used to differentiate normal squamous epithelium from abnormal inflammatory or neoplastic squamous epithelium, or metaplastic epithelium such as the columnar epithelium of Barrett's esophagus (Figure 4). The largest use of Lugol's solution is in identifying dysplastic or malignant squamous epithelium. While large malignancies



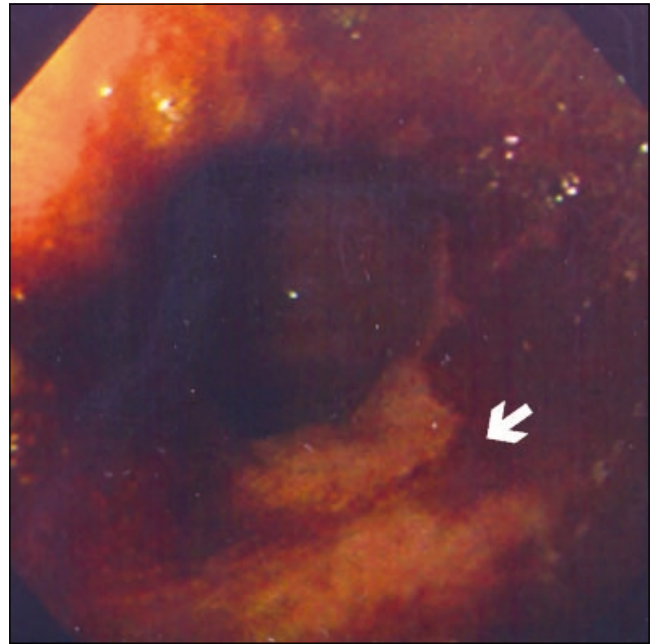


**Figure 3)** Proximal and distal India ink tattoos in the colon

of the esophagus are readily identifiable, early lesions or the full extent of the malignant involvement is not always evident at the time of endoscopy. Lugol's solution can be used to identify early subtle neoplastic esophageal processes, as well as stage more accurately the extent of mucosal involvement. When identifying esophageal cancer, 20 to 50 cm<sup>3</sup> of a 1% to 50% solution was used.

While Lugol's iodine has not been studied as extensively for this purpose, it should also be able to detect, by negative staining, inflammatory esophageal epithelium that has fewer intact glycogen-containing cells. Similarly, small, previously unrecognized areas of columnar epithelium can be observed as a negative stain following installation of Lugol's solution into the esophagus. Woolf and co-workers (13) determined that the sensitivity of Lugol's solution was 89% and the specificity 93% when used for this purpose. Lugol's solution has also been used alone or in conjunction with Indigo carmine and magnification endoscopy to increase the recognition of short segments of Barrett's esophagus. This has potential screening and therapeutic implications, and may become more applicable now that endoscopic techniques are being actively investigated to attempt to eradicate Barrett's esophagus.

More recently, the absorptive characteristics of methylene blue have been used to identify the specialized columnar epithelium of Barrett's esophagus, in order to increase the accuracy of endoscopic biopsies (14). Canto and colleagues (14) determined that a 0.5% solution of methylene blue (following installation of 10% solution of *N*-acetylcysteine) had an accuracy of 95% in detecting specialized columnar epithelium of Barrett's esophagus. The controls in that study had a diagnostic yield of 45%, implying that Barrett's esophagus was routinely missed. Ninety-five per cent of



**Figure 4)** Unstained mucosa (arrow) of the esophagus following application of Lugol's solution. Biopsy revealed Barrett's mucosa that was otherwise unrecognized

stained specimens demonstrated specialized columnar epithelium versus 3.5% of nonstained biopsies. This staining was reproducible at eight weeks, and dysplasia was stained as well. The risk of dysplasia in a stained biopsy specimen had an odds ratio of 17.7 ( $P=0.0004$ ). This technique, which is easily performed, deserves further scrutiny because it may allow improved accuracy of endoscopic screening and surveillance of Barrett's esophagus.

Tattooing has also been used in the esophagus. India ink tattoos have been applied to insure precision of measurement, relocalization and rebiopsy of specific sites. This is, in part, in response to the imprecision of standard endoscopic measurements. India ink tattooing of the esophagus was first reported in 10 patients as part of a Barrett's esophagus eradication trial using bipolar probe therapy (BICAP, Circon ACMI, Connecticut) (15). Since then, Shaffer and colleagues (12) studied 19 patients after 0.1 mL of India ink, diluted in a one to 10 ratio with normal saline, was used to demarcate the proximal extent of Barrett's esophagus. Follow-up at three, nine, 15, 24 and 36 months revealed a 95% persistence of the tattoo at three months. All 15 patients evaluated at 36 months had persistence of good to excellent tattooing with this agent. There were no complications or side effects, and in nine cases biopsies showed persistence of the carbon particles without inflammatory response.

**Stomach:** Methylene blue has been studied extensively as a means of staining gastric intestinal metaplasia (3,4,6,16). Once surface mucus is removed with a mucolytic agent and methylene blue is applied, islands of methylene blue staining epithelia are easily identified. A variety of staining forms have been described: focal versus diffuse and subtle versus prominent. The more prominent stains correlate to a greater

'density' of goblet cells seen on pathological examination. Theoretically, staining the gastric intestinal metaplasia with methylene blue should allow quantification of the amount of gastric involvement by intestinalized epithelium, as well as longitudinal follow-up to establish the natural history of the lesion as well as, for example, its response to anti-helicobacter therapy. Most recently, methylene blue has been used in the stomach to map intestinal metaplasia of the cardia (16). In that study, the use of methylene blue increased the recognition of this lesion.

Congo red and phenol red can be used to map acid-secreting and alkaline areas of the stomach. In the past, Congo red was used to assess the adequacy of a surgical vagotomy. Congo red has also been used in combination with methylene blue to identify dysplasia in the stomach ('bleached areas' not stained with methylene blue or Congo red). Phenol red has been used to identify alkaline areas within the stomach. Dense colonization of *H pylori* can be identified by this technique because the local production of ammonia by the organisms results in a local alkaline pH.

**Small bowel:** The absorptive dye methylene blue has been used to identify metaplastic gastric epithelium in the duodenal bulb by negative staining (7). The most common clinical and research application of tissue staining in the small bowel has been the use of contrast agents in the identification of celiac sprue. It is estimated that the prevalence of sprue is as high as one in 230 people of European decent. The spectrum of illness ranges from the asymptomatic individual to a life-threatening malabsorptive process. The diagnosis of sprue remains histological, but certain endoscopic markers such as scalloping of the mucosa, loss of duodenal folds and a mosaic mucosal appearance increase the likelihood of sprue being present. The sensitivity and specificity of these endoscopic findings are 94% and 92%, respectively. However, these endoscopic appearances may be subtle, absent or unrecognized. Dye spraying has been used to facilitate the delineation of this surface morphology (17,18). Indigo carmine as a contrast agent was used as early as 1976, and in a more recent study was significantly more effective when combined with a magnifying endoscope than standard endoscopy in identifying partial atrophy characteristic of sprue (17). This technique was 91% accurate versus 9% with a standard endoscope without dye spraying ( $P < 0.01$ ). Methylene blue has also been used as a small bowel contrast agent. In a video-endoscopic study, the kappa value for identifying the loss of folds with this technique was 0.59, and for scalloping was 0.76.

**Colon:** Tissue staining has been best studied in the colon as a means of identifying small or flat neoplastic polyps that otherwise would go unrecognized (19-22). Tissue staining has also been used in the surveillance of ulcerative colitis (23-24), and in tattooing of polypectomy sites for surgical re-localization, once a polyp is found to be malignant (10). It also has other potential applications.

Identifying whether a patient is an adenoma former has clinical implications for further endoscopic surveillance recommendations, yet endoscopists are aware that small polyps

may be difficult to identify and are missed frequently at the time of colonoscopy. Furthermore, some investigators have noted that small, flat adenomas (which may be very difficult to detect) have an increased incidence of dysplasia and of malignancy. Thus, enhanced recognition of small lesions may be clinically relevant.

Numerous studies have established that chromoendoscopy enhances the visualization of diminutive colonic lesions. Mitooka and colleagues (20) compared indigo carmine and magnifying endoscopy with standard endoscopy, and demonstrated enhanced detection as well as visualization of flat lesions (7.7% versus 1.8%). Thus, chromoendoscopy was shown for the first time not only to enhance the appearance of recognized lesions, but also to increase the yield of detection. Matsumoto et al (23) also detected four cases of minute (2 to 4.5 mm) flat lesions that contained invasive cancer, detected by chromoendoscopy, with a 1% to 2% solution of indigo carmine. Because of this observation, they have routinely used dye spraying of the entire colorectal mucosa since 1990. Others have also demonstrated that the accuracy of detection of small lesions is increased with dye spraying (16). More recently, Axelrad and colleagues (22) used dye spray combined with magnifying endoscopy to differentiate adenomatous polyps from hyperplastic polyps (22). The overall accuracy of this technique was 82%, based on differences in surface characteristics of the lesions observed with dye spraying. Cresyl violet has also been used as a chromoendoscopy agent in similar studies of the colon.

Dye spraying or chromoendoscopy has also been used in ulcerative colitis to quantify inflammation and detect early neoplasia (23,24). Both indigo carmine and cresyl violet have been used to detect the lack of a normal mucosal 'network pattern' and crypt openings, which correlate with inflammatory activity and histology. Indigo carmine dye spraying was also used in 85 patients with ulcerative colitis undergoing surveillance examinations. Thirty-two were found to have flat polyps, and 19% of these were neoplastic (24). These lesions were ill-defined before dye spraying.

Tattooing of the colon has also been described extensively. Tattooing is clinically applicable to mark the site of a possible malignant polyp, and to follow lesions longitudinally in vivo. Tattooing with India ink has been safe and without side effects, but systematic studies are lacking (10). Shatz and colleagues (11) followed 54 patients with India ink tattoos for 1.5 to 117 months. All tattoos persisted without symptoms or complications, and in 84 biopsies, 78 were without inflammation. Six biopsies demonstrated only mild inflammation; five of these were studied six months later, with three having no residual inflammation. Results from this and other reports of nearly 200 patients with colonic tattoos indicate that India ink is not only durable but also safe.

## CONCLUSIONS

Chromoscopy has many uses as an adjunctive technique during gastrointestinal endoscopy. This technique is underused clinically, and its full clinical and research applicability is yet

to be determined (2). Appropriately designed and implementable outcomes studies will determine the place tissue staining has in endoscopic practice.

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