compared with only 27% of patients failing therapy. Thus the authors suggested that clinicians should adjust AZA or 6-MP doses to achieve erythrocyte 6-TGN concentrations $>235 \text{ pmol}/8 \times 10^8 \text{ RBCs}$. These findings have not been universally confirmed. Two recent studies showed no relationship between disease activity and whole blood 6-TGN concentrations in 170 adults and 55 children with IBD treated with AZA or 6-MP.^{10, 11} In another recent pilot study, direct administration of thioguanine resulted in median erythrocyte 6-TGN concentrations of $1045 \text{ pmol}/8 \times 10^8 \text{ RBCs}$ without uniformly achieving efficacy or toxicity, suggesting that the relationship between 6-TGN concentrations and both efficacy and toxicity is indirect.¹² In the study by Cuffari and colleagues¹³ in this issue of *Gut*, non-responding patients with IBD treated with very low doses of AZA (1.1 (0.1) mg/kg) who did not have leucopenia and who had "subtherapeutic" 6-TGN concentrations had their AZA doses gradually increased to a mean of 1.5 (0.1) mg/kg/day, with subsequent clinical response and increase in 6-TGN concentrations in many patients (see page 642). It is likely that the same result could have been achieved by simply administering doses of AZA that have been proved to be efficacious in Crohn's disease in controlled trials (2–3 mg/kg/day) from the outset, without therapeutic drug monitoring. The utility of routinely measuring 6-TGN concentrations in clinical practice remains unclear.

How then should practising clinicians use the available evidence to treat patients with AZA or 6-MP? Patients should routinely be tested for TPMT activity (phenotype) or genotype prior to initiating AZA or 6-MP therapy. Patients with normal TPMT activity or the wild-type genotype should receive drug doses that have been proved to be efficacious in controlled clinical trials (AZA 2–3 mg/kg/day or 6-MP 1.5 mg/kg/day). Patients with intermediate TPMT activity or the heterozygote genotypes should initially have an empiric reduction of 50% in drug dose (AZA 1–1.5 mg/kg/day or 6-MP 0.75 mg/kg/day). Patients with absent TPMT activity or the homozygous low activity genotypes should only be treated with great caution at very low doses (approximately 10% of the standard dose), and perhaps not at all. Clinicians should expect that the clinical effect of AZA or 6-MP will be reached over approximately 1–2 months. Routine therapeutic drug monitoring of

6-TGN in patients being treated with AZA or 6-MP is not necessary but can be considered in selected settings: patients suspected of non-compliance; patients receiving allopurinol; patients with intermediate or low TPMT activity; and possibly patients who are failing to respond to standard doses of drug. Less experienced clinicians who are uncomfortable prescribing the full standard doses of AZA or 6-MP proven to be effective in clinical trials may be reassured by the laboratory finding of a "subtherapeutic" 6 thioguanine concentration and subsequently be convinced to increase the drug dose, similar to the experience reported by Cuffari *et al.*

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See article on page 683

New pouches for old?

It is now 25 years since the ileal pouch procedure was introduced for patients with ulcerative colitis and familial adenomatous polyposis, holding out the promise of life without a permanent ileostomy. As time has gone by the procedure has been modified, refined, and the indications widened until the present situation where most teams use an almost standard stapled pouch and pouch anal anastomosis. The technique has been simplified to such an extent that surgeons outside specialist centres are comfortable offering the operation. But problems remain. A tiny cuff of columnar epithelium is left behind¹ which can potentially become inflamed or undergo malignant change.² Also, however perfect a postoperative course, there is still a minority of patients who have poor function, whether unacceptable frequency, episodes of leakage, or of course pouchitis.

And now, along comes a new operation, which Andriesse *et al* have termed *ileo neo-rectal anastomosis* (INRA) and described in this issue of *Gut* (see page 683).³ How does it shape up to the existing competition and are there any theoretical advantages or disadvantages?

The new operation preserves the patient's existing rectal muscle wall. The mucosa is painstakingly stripped off the underlying muscle of the lower half of the rectum, much as in the very early days of pouch surgery. Into this muscle tube is inserted an ileal mucosal mesh made by removing its muscle coat over the last 15 cm or so of distal ileum, preserving a couple of strips of muscle wall to act as a skeleton (see fig 1 in Andriesse and colleague³). The far end is hand sewn endoanally to the dentate line and the mucosa meshed with multiple criss cross incisions to increase its surface area. It is then pressed into place to fill out and adhere to the denuded rectum with a pack for two days. A covering loop ileostomy is raised.

As a technical exercise this is clearly a demanding procedure and has many reminders of the pioneering years of pouch surgery. Firstly, there is a hand sewn anastomosis

and the inevitable anal dilatation, which may impair continence. In expert hands this can be minimised but there is still a tendency to more nocturnal seepage. The creators of restorative proctocolectomy believed that a long rectal muscular cuff was essential for the sensation of pouch filling, but we now know that stretch receptors lie within the pelvic floor muscles. Pouch patients with an anastomosis to the top of the anal canal with hardly any rectal muscle cuff can feel and empty satisfactorily.

The long mucosectomy needed to strip a sizeable cuff can be difficult and incomplete. Tiny islands of remaining mucosa not amenable to surveillance increase the risk of cuff abscess and the inevitable poor function, and later malignant change. Of the published cases of cancer complicating pouches, the majority are in those who have had a mucosectomy.¹

While theoretically elegant, there is no evidence that preserving the rectal wall and putting on an ileal mucosal graft improves function. As day and night time stool frequency declined, sensation, pressures, and anal integrity were preserved and rectal compliance improved with time, but these are changes seen with a conventional pouch procedure. Overall stool frequency was higher than reported for J pouches⁴ and even after preserving the rectal wall, recto-anal inhibitory reflexes were not maintained.⁵

One of the arguments against ileorectal anastomosis in ulcerative colitis is the long term effect of repeated inflammation on rectal compliance. A narrow stiff fibrotic rectum would probably remain so after mucosectomy and INRA. This would have implications for case selection favouring "mild" cases and ruling out those with dysplasia or established rectal cancer. Indeterminate colitis and Crohn's disease would be worries too.

Three of the 11 cases developed what the authors have chosen to call neoproctitis. As the meshed mucosa grows over the denuded rectal wall there will be healing and degenerative changes but once complete the ileal mucosa would become analogous to pouch mucosa. It is not clear why the authors have chosen not to call this pouchitis and use the well established histopathological definitions and scoring systems. This would allow an easier comparison between the two techniques but it is obvious that INRA patients also develop pouchitis.

Although the INRA approach may have theoretical advantages over the established pouch operation, there is no evidence that any of these have been fulfilled. It is likely to be a more difficult procedure with higher morbidity and just now, it seems inappropriate for patients to be exposed to these added risks.

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