● USE OF A NOVEL MARKER FOR DIFFERENTIATING GASTRIC INTESTINAL METAPLASIA.

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Gastric intestinal metaplasia (IM) is a condition of uncertain pathogenesis, with some increased risk of carcinoma over the general population, but much less so than for intestinal metaplasia of the esophagus or Barrett's epithelium (BE). This may be due to the heterogeneity of IM in the stomach. While gastric IM can be easily diagnosed by routine H&E staining, there is no clear marker for predicting which cases may have an increased risk for the development of dysplasia/cancer. Special mucin stains including alcian blue/high iron diamine have been utilized to differentiate various forms of gastric IM. We developed a monoclonal antibody (moAb) 7E12H12 (IgM isotype) that reacts specifically with specialized columnar epithelium of the esophagus (BE) and colon epithelium, but not with normal epithelium from esophagus, stomach and small intestine (Ann Int Med 120:753, 1994). **OBJECTIVE:** In this study we have attempted to ascertain the reactivity rate of 7E12H12 moAb with gastric IM and compare the results with standard alcian blue staining. **METHODS:** 53 cases of gastric IM diagnosed by routine H&E staining from RWJUH and MRMC were obtained. All were tested by a sensitive immunoperoxidase method using 7E12H12 moAb. 39 of these were also tested by alcian blue/high iron diamine staining. **RESULTS:** All 39 samples tested by alcian blue/high iron diamine were positive for reactivity against IM whereas 7E12H12 reactivity was evident only in 10. Of the total 53 samples tested by 7E12H12 alone, only 13 (24.5%) were reactive to metaplastic cells. **CONCLUSION:** Whereas alcian blue stained all IM in the stomach, the moAb reacted more selectively. Further studies are needed to correlate the 7E12H12 reactivity with the type of metaplasia. 7E12H12 may detect cases of colonic type, or "incomplete gastric IM" which are thought to be prone to the development of dysplasia/adenocarcinoma.

● **RECTAL GLUTATHIONE CONTENT AND GLUTATHIONE-S-TRANSFERASES ACTIVITY IN X-LINKED AGAMMAGLOBULINAEMIA (XLA) PATIENTS. A COMPARISON WITH HEALTHY VOLUNTEERS AND PATIENTS WITH ADENOMAS.**

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XLA is a primary immunodeficiency disorder. An increased risk for developing cancer is well established in late-onset agammaglobulinaemia and less well in XLA. We noticed a 30-fold greater incidence of rectosigmoid cancer in patients with XLA than in the normal population (Lancet 1993;341:1439-40). Glutathione (GSH) and GSH-related enzymes are involved in the metabolism and detoxification of cytotoxic and carcinogenic compounds. Tissues with low or reduced levels of GSH and glutathione-S-tranferases (GST) activity may have a reduced capacity to detoxify carcinogens, resulting in more cytogenetic damage, which could lead to a higher tumor risk. A significant negative correlation exists between GST-activity in the mucosa along the gastrointestinal tract and tumour incidence in humans (Br J Cancer 1993;67: 1413-17).
Aim and methods. We investigated GSH content and GST-activity in normal rectal mucosa of XLA-patients (n=8), healthy volunteers (n=10) and patients with recently removed colonic adenoma(s) (n=10). Differences between groups were assessed by the Mann-Whitney U test.
Results. Values are given as means ± SEM.

	Age (yrs)	GSH (nmol/mg protein)	GST-activity (nmol/min/mg protein)
XLA	34 ± 2	50 ± 2	143 ± 17[#]
Adenoma	49 ± 3	41 ± 2[*]	233 ± 20[@]
Normal	24 ± 1	44 ± 1	321 ± 30

[*]: $p<0.02$ compared to XLA, [#]: $p<0.01$ compared to adenoma and normal, [@]: $p<0.05$ compared to normal.
Conclusion. The rectal GSH content in XLA-patients and patients with adenomas is not statistically different from healthy controls. Patients with adenomas have a significantly lower rectal GST-activity compared to healthy volunteers whereas GST-activity of XLA patients is even lower. These findings indicate that in XLA patients the risk of colorectal cancer might partly be explained by a lower detoxification capacity in the mucosa.

● **THE EFFECT OF RESISTANT STARCH ON COLONIC PROLIFERATION (PCNA), FAECAL BILE ACIDS AND SHORT CHAIN FATTY ACIDS IN PATIENTS WITH COLONIC ADENOMAS: A CONTROLLED TRIAL.**

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Resistant Starch (RS) is fermented in the large bowel, resulting in the production of short chain fatty acids (SCFA), CH_4 and H_2. Possibly through acidification of colonic contents the formation of cytotoxic secondary bile acids and colonic mucosal proliferation has been shown to decrease subsequently in healthy volunteers (Dig Dis Sci 1994;39:834-842). These intermediate biomarkers may play a role in colonic carcinogenesis. RS seems to influence these biomarkers in a favourable way. *Aim.* We therefore studied the effect of supplementation of Hylon VII (45 gram/day) to a normal Dutch diet on patients (pts) with recently removed adenoma(s) in a controlled trial. Hylon VII is a high amylose maize starch, containing 62% RS. Glucose (G) was used as placebo. *Methods.* Twentythree pts (12♂, 11♀) consumed 45 gram of G /day during four weeks. After this period pts were randomly assigned to either Hylon VII (7♂, 6♀, mean age 57.8, BMI 26.7 ± 1.3 kg/m²) or G (5♂,6♀, mean age 56.8, BMI 24.8 ± 0.8 kg/m²) for another four weeks. At 4 and 8 weeks rectal biopsies and 48 hours faeces were collected. Differences in delta's (δ) between 4 and 8 weeks of both groups were assessed by Mann-Whitney U test. *Results.* The PCNA (Proliferating Cell Nuclear Antigen) labelling index in rectal biopsies was not influenced by RS intake (δ G: +1.3, δ RS: -0.1%, p=0.73). The faecal wet and dry weight as well as the pH, the total SCFA concentration and excretion did not change significantly in the RS group. The total faecal soluble bile acid concentration decreased in the RS group (δ G: +2.6, δ RS: -29.7 μmol/l, p=0.05). The concentration and percentage primary bile acid increased (resp. δ G: -14.2, δ RS: +11.6 μmol/l, p=0.05 and δ G: -5, δ RS: +16%, p=0.001) and the percentage secondary and dihydroxy bile acids decreased (resp. δ G: +6, δ RS: -16%, p=0.002 and δ G: -2, δ RS: -12%, p=0.01) in the RS group. No changes in dietary composition were observed during the study period. *Conclusion.* These results partly confirm our previous observations in healthy subjects (bile acids), but are at odds with respect to the SCFA excretion and colonic cell proliferation. A possible explanation can be found in a relatively higher basal fibre and lower fat intake in these patients, compared to the previously studied healthy subjects.

● GENETIC INSTABILITY AND CLINICOPATHOLOGICAL FEATURES OF COLORECTAL CANCER IN YOUNG PATIENTS.

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Background: A significant proportion of colorectal cancers (CRC) in young patients may be due germline mutations in mismatch repair genes as demonstrated by microsatellite instability (MIN). Recent studies suggest that sporadic CRC with MIN exhibit a number of distinct clinicopathological features. **Purpose:** To determine the frequency and clinicopathological relevance of MIN in CRC from young patients. **Methods:** Twenty-five patients ≤35 years old (average age=30.7 years) with CRC in whom Familial Adenomatous Polyposis was excluded, were identified from the population-based Ontario Cancer Registry. Paraffin-embedded specimens were histologically reviewed, CRC of >70% cellularity and normal mucosa were microdissected and digested, DNA amplified by PCR with $\gamma^{32}P$ at 5 $(CA)_n$ microsatellites (D2S123, D5S346, D7S519, D11S904 & D17S787), separated by denaturing gel electrophoresis and exposed to film. **Results:** MIN was seen in 12 of 25 CRC patients, 7 of which displayed MIN at ≥2 loci. Loss of heterozygosity of the chromosome 5 or 17 microsatellite occurred in 6 of the tumors. Six of 12 CRC with MIN and 6 of 13 CRC without MIN occurred proximal to the splenic flexure. Synchronous adenomatous or hyperplastic polyps were noted in 6 patients without MIN, while only 1 patient with MIN had a synchronous polyp. Patients with CRC exhibiting MIN and those without were similar for Dukes staging and survival at an average follow up of 3.2 years. CRC with MIN was more likely to be poorly differentiated (MIN+ 50% vs. MIN- 15%), or exhibit peritumoral (MIN+ 92% vs. MIN- 50%) or intratumoral (MIN+ 83% vs. MIN- 58%) lymphocytic infiltration. The occurrence of MIN in CRC was unrelated to other pathological features previously described in hereditary nonpolyposis CRC (HNPCC) such as extracellular mucin production, Crohn's-like lymphoid reaction or expansile tumor margins. **Conclusions:** MIN is very common in CRC in young patients, suggesting that defects in mismatch repair are important in the pathogenesis of these tumors. The presence of MIN in CRC in this young age group correlates strongly with some pathological features of HNPCC. However, the relationship of the molecular phenotype of MIN to other features of HNPCC remains unclear.