SOME OBSERVATIONS ON COLORECTAL POLYPS; ONLY CONCERNS THOSE WHO HAVE A COLON.

Dr Castleman – Harvard

- In 1951 Dr. Benjamin Castleman succeeded Dr. Mallory as Chief of Pathology and Editor of the Case Records of the Massachusetts General Hospital in NEJM.
- Castleman’s disease of lymph nodes.
- Armed Forces Institute of Pathology fascicles on tumors of the thymus and parathyroid glands.
- Dr. Castleman’s former residents created the Benjamin Castleman Award, which is presented annually at the meeting of the United-States-Canadian Academy of Pathology to a young pathologist who has performed outstanding research.

NEJM 1962; 267: 469-475

- Castleman re-evaluated polyps that had been believed to contain cancer from another study. Essentially no follow-up.
- Concluded “The overwhelming majority of cancers in the colon arise as cancer de novo or in villous adenomas, not in adenomatous polyps. The adenomatous polyp is a lesion of negligible malignant potential.”
Two Australians win Nobel Prize in Medicine
Awarded for work on peptic ulcer disease

NEJM, Cont

- 1418 patients had a complete colonoscopy during which one or more adenomas of the colon or rectum were removed.
- Follow-up colonoscopy [average 5.9 years]
- Colorectal cancer [CRC] incidence compared with that in 3 reference groups: 2 cohorts in which colonic polyps were not removed and one general-population registry adjusted for sex, age, polyp size.

Cont

- 5 asymptomatic early-stage CRC (malignant polyps) detected by colonoscopy (3 at 3 years, one at 6 years, and one at 7 years). No symptomatic cancers were detected.
- The numbers of CRC expected on the basis of the rates in the three reference groups were 48.3, 43.4, and 20.7, for reductions in the incidence of colorectal cancer of 90, 88, and 76 percent, respectively (P < 0.001).

What are Colorectal Cancer Screening Guidelines for Average Risk People [United States]?

- Starts at age 50
- Annual fecal occult blood test [FOBT] Or fecal immunohistochemical test [FIT]
- OR annual FOBT and flexible sigmoidoscopy
- OR double contrast barium enema every 5 years
- **OR colonoscopy every 10 years**
Post-Polypectomy 2008 Guidelines

1. **Patients with small rectal hyperplastic polyps** should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be **10 years**.

2. **Patients with only one or two small (<1 cm) tubular adenomas with only low-grade dysplasia** should have their next follow-up colonoscopy in **5 to 10 years**.

3. **Patients with 3 to 10 adenomas, or any adenoma > 1 cm, or any adenoma with villous features, or high-grade dysplasia** should have their next follow-up colonoscopy in **3 years**.

4. **Patients who have more than 10 adenomas at one examination** should be examined at a shorter (3 years) interval established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome.

5. **Patients with flat/sessile adenomas that are removed piecemeal** should be considered for follow up at short intervals (2 to 6 months) to verify complete removal.

6. **More intensive surveillance is indicated when the family history may indicate hereditary nonpolyposis colorectal cancer.**
How Common are Colorectal Polyps?

• In Western countries – about 50% of people will develop an adenoma in their lifetime.
• About 10% of such lesions destined to progress to carcinomas.

Why so many cancers when we can screen?

• In the US, Medicare began to cover screening colonoscopy in 2001 for average risk persons.

Cancer Stats Estimates for 2009, Colorectal Cancer [Jemal]

• Colon Cancer - New Cases – 106,100
• Rectal Cancer – New Cases – 40,870
• TOTAL – 146,970
• Deaths [Colon and rectum]– 40,920 [24,260 M, 25,700 F]
• 2003 estimates -154,500 new cases, 57,100 deaths
• 2000 estimates – 130,200 new cases, 56,300 deaths
Cancer Stats Estimates for Colorectal Cancer [Jemal]

Screening, California, 2001

• 2001 California Health Interview Survey (CHIS 2001)
• Random-digit dial telephone survey that was conducted in California.
• 22,343 adults age ≥ 50 years.
• Nearly 54% of California adults reported receipt of a recent CRC test.
• Insurance coverage and having a usual source of care were the most important predictors of CRC testing.

California, Cont

• Latinos age < 65 years were less likely to be tested than whites.
• Men were more likely to be tested than women.
• Women were more likely than men to say that their physician did not inform them the test was needed and that CRC tests were painful or embarrassing.
Another problem

• Many women simply do not have colons – some do not even have a GI tract at all.

Screening, Canada

Canada - colon screening has been free for years, but still [in a 2007 paper] only about 14% of average risk adults undergo screening; huge factor is whether their primary physicians suggest it.


- Case control study of patients diagnosed with colorectal cancer between 1996-2001 and died by 2003
- Of 10,292 cases [people who were dead of colorectal cancer], 7% had previous colonoscopy
- Among 51,460 controls, 9.8% had previous colonoscopy
- Colonoscopies performed between 1/1/1992 and 6 m prior to dx of CRC

Canadian Study

- Odds ration for association between complete colonoscopy and CRC reduction was **0.33 for left-sided lesions**
- **0.99 for right sided lesions**

Why???

- Colonoscopy was performed by non gastroenterologists 69% of the time
- **NO ONE KNEW HOW TO RECOGNIZE RIGHT SIDED PRECURSORS ENDOSCOPICALLY OR HISTOLOGICALLY**
- The hope – we will do better in a few more years [although this study is different from prospective method]
Two Kinds of Colon Cancer

- The regular kind
- The kind associated with mismatch repair defects
- Syndromic examples studied first

Incidence of FAP, HNPCC, and Sporadic CRC
The Regular Kind of Colon Cancer
Syndromic and Sporadic
The Fearon/Vogelstein Model of Multistep Carcinogenesis

<table>
<thead>
<tr>
<th>CHROMOSOME</th>
<th>5q</th>
<th>12p</th>
<th>18q</th>
<th>17p</th>
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<tbody>
<tr>
<td>GENE</td>
<td>APC</td>
<td>k-ras</td>
<td>DCC, DPC4</td>
<td>p53</td>
</tr>
<tr>
<td>FUNCTION</td>
<td>transcription factor</td>
<td>G-protein</td>
<td>Cell adhesion molecule</td>
<td>Transcription factor</td>
</tr>
<tr>
<td></td>
<td>factor</td>
<td>protein</td>
<td>molecule</td>
<td>Other</td>
</tr>
<tr>
<td>Mutations</td>
<td></td>
<td></td>
<td></td>
<td>Mutations</td>
</tr>
</tbody>
</table>

- Normal Epithelium
- Early Adenoma
- Intermediate Adenoma
- Late Adenoma
- Carcinoma
- Metastasis

Fearon and Vogelstein, Cell, 1990
APC-Adenomatous Polyposis Coli gene

• Tumor Suppressor Gene, chromosome 5q, fits Knudson's two-hit hypothesis for tumor suppressor genes.
• FAP families—Affected members have one allele mutated in germline, 2nd hit occurs in the tumor.
• Sporadic—Both alleles inactivated somatically.
• Mutated very early during sporadic or FAP CRC carcinogenesis.
• Normally binds to and promotes degradation of β-catenin (transcription factor) in the cytoplasm.
• With APC mutation, β-catenin is unchecked, migrates to nucleus, activates c-myc, etc.

The Other Kind of Colorectal Cancer
Syndromic and (?) Sporadic
Historic Hereditary Non-Polyposis Colorectal Cancer (HNPCC): Aldred Warthin

1895: "I will die at an early age from cancer of my colon or female organs because most of my family members die of these cancers", Aldred Warthin's seamstress prior to her death of endometrial cancer. Published Family G in 1913.

HNPCC [Hereditary Non-Polyposis Colorectal Cancer] Features

- Mean Age: 44 years
- Inheritance: autosomal dominant
- Site: 70% proximal to splenic flexure, though 30% distal!
- Penetrance: >90%
- Histology: more likely-poorly differentiated, mucinous, signet ring cells, intense lymphoid infiltrates
- Defect: unknown in 1993
- First Clue: serendipitous discovery of microsatellite instability
- ACCOUNTS FOR ABOUT 1-2% OF CRC

Microsatellite DNA

Unit Size: 1-6 bp (e.g. A, CA, CAG, AT)
#Units/ microsatellite: 10-60, e.g. (CA)$_{10}$

CACACACACACACACACACACA
Genomic Copies: 50-100K
Gene Localization: Non-coding (between genes, introns)
Polymorphism: Extremely high (some >10 alleles)
Variability: Low, germline pattern is fixed at birth and present in all tissues
Applications: Gene Mapping, Forensics

The repeated sequences of microsatellites prone to errors in replication
Microsatellite Instability (MSI, MIN) = RER (Replication ERror)

MSI: Novel length alleles in tumor compared to the patient's germline

Germline (e.g. Lymphs)  "Normal" Tumor  RER/MSI Tumor

**Found serendipitously when doing gene mapping for HNPCC** Thibodeau, Vogelstein, Perucho

Mismatch Repair (MMR, bacteria)

Genes involved in HNPCC

<table>
<thead>
<tr>
<th>Bacterial MMR Homologue</th>
<th>Human Gene</th>
<th>Chromosomal Localization</th>
<th>Germline Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MutS</td>
<td>MSH2</td>
<td>2p21</td>
<td>157 (39%)</td>
</tr>
<tr>
<td></td>
<td>MSH6</td>
<td>2p21</td>
<td>31 (8%)</td>
</tr>
<tr>
<td>MutL</td>
<td>MLH1</td>
<td>3p21-23</td>
<td>200 (50%)</td>
</tr>
<tr>
<td></td>
<td>PMS2</td>
<td>7p22</td>
<td>5 (1%)</td>
</tr>
</tbody>
</table>
MSI-Hi CRC with PMS2 Loss

MSI-HI CRC – Many TILs

CD3, MSI-Hi CRC
“Medullary” CRC in HNPCC
Testing in HNPCC, and sporadic MMR defective tumors

- Strength of family history (Amsterdam criteria), 3-2-1 Rule
  - 3 relatives with histologically confirmed CRC
  - 2 successive generations
  - 1 must be a first degree relative of the other two
  - 1 must be <50 years old
- Location of the tumor, classic histologic features
- Bethesda Criteria for MSI testing

Bethesda Criteria for MSI Testing

1. CRC diagnosed before age 50y
2. Multiple CRC or HNPCC-related cancers [endometrium, small bowel, pelviureter, biliary tract, stomach, ovary, pancreas, brain [GBM]]
3. CRC or HNPCC related cancer WITH MSI - RELATED HISTOLOGY diagnosed before age 60 [TILs, Crohn’s-like lymphoid reaction, mucinous/signet cell differentiation, medullary pattern]

Bethesda Criteria for MSI Testing, cont’d.

4. CRC or HNPCC-related cancer diagnosed in at least one first-degree relative before 50 y
5. CRC or HNPCC-related cancer diagnosed in at least 2 first – or second-degree relatives at any age.
Loss of MLH1 in CRC

Retained MSH2 in CRC

49 year old man with colon and prostate cancer
• If colorectal adenomas are the precursor to microsatellite stable colorectal cancer, what is the precursor to microsatellite unstable cancer?
• We thought they came from nowhere not long ago.
65 year old woman.
Ascending colon polyp.
Described as ?thickened fold versus ?Flat adenoma by endoscopist

Sessile Serrated Adenoma
Superficially resembles a hyperplastic polyp but differs by having broad-based crypts, serrations to the bases of the crypts, frequent right sided location. These polyps are “precursor lesions”
Torlakavic and Snover – “SSA”

**Dilatation of Crypts**

Published Example

*Torlakavic and Snover, Gastroenterology 1996;110:748-755*

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Torlakavic and Snover – “SSA”

**Horizontal Crypts**

Published Example

*Torlakavic and Snover, Gastroenterology 1996;110:748-755*

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Torlakavic and Snover – “SSA”

**Decreased Endocrine Cells**

This is from a “usual” HPP with increased endocrine cells

*Torlakavic and Snover, Gastroenterology 1996;110:748-755*
Torlakavic and Snover – “SSA”  
**Nuclear Atypia**

Control HPP  
“Sessile SA”

Torlakavic and Snover, Gastroenterology 1996;110:748-755

Torlakavic and Snover – “SSA”  
**Focal Mucin Overproduction**

Mimics stomach

Goblet cells extend to the base

Torlakavic and Snover, Gastroenterology 1996;110:748-755

Torlakavic and Snover – “SSA”  
**Mid to Upper Proliferation Zone**  
(An Unpublished Example)

O = Mitotic Figures

Torlakavic and Snover, Gastroenterology 1996;110:748-755
Regular left-sided teensy hyperplastic polyp
?Sporadic Counterpart to HNPCC

- About 15% of sporadic colorectal cancers have mismatch repair defects in the tumor [MSI-hi]. [About 2% of all CRC are HNPCC-related.]
- The genetic mechanism is a little less analogous than in adenomas/FAP
- The sporadic tumors often have promoter methylation of MLH1 rather than biallelic inactivation by mutations

*Sporadic Counterpart to HNPCC

<table>
<thead>
<tr>
<th>GENE</th>
<th>BRAF</th>
<th>kras</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Epithelium</td>
<td>Early Serrated polyp</td>
<td>“Villosity” in Serrated polyp</td>
</tr>
<tr>
<td>Methylation</td>
<td>HMLH1/MGMT Methylation</td>
<td></td>
</tr>
</tbody>
</table>

Various authors

*****CpG Island Methylator Phenotype

*CIMP=CpG Island Methylator Phenotype

A. BRAF Serrated Polyp Pathway

B. KRAS Serrated Polyp Pathway

CIMP=CpG Island Methylator Phenotype
Polyps like this are precursors to at least a subset of [sporadic] MSI-hi colorectal cancer

When colon polyps were simple
• There were adenomas
• There were hyperplastic polyps
• Any fool could easily tell them apart
No Grey Zone Between Hyperplastic Polyps and Adenomas

Cross SS et al. What levels of agreement can be expected between histopathologists assigning cases to discreet nominal categories? A study of the diagnosis of hyperplastic and adenomatous colorectal polyps. Mod Pathol 2000; 13: 941-944.

• **0.84-0.98 kappas!**
What About Kappas for This Polyp?
67 y/o woman, 17 mm ascending colon polyp, completely resected

Subtle example, With slightly dilated, slightly branched deep crypts

SSA's in “HPPosis”
J.G., 66 y/o woman, right colon

J.G., 66 y/o woman, right colon
Polyp #1, 1.4 cm

Sessile architecture

Dilated, horizontal spread

Serrations at base
J.G., 66 y/o woman, right colon
Polyp #2, 1.3 cm
Dilated crypts,
Deep branching
Extension deep
thru musc. mucosae

J.G., 66 y/o woman, right colon
Polyp #2, 1.3 cm
Gastric type mucinous epith.
Dysplastic goblet cells?

J.G., 66 y/o woman, right colon
Polyp #3, 1.2 cm
Dilated crypt, horizontal spread
J.G., 66 y/o woman, right colon
Polyp #4, 1.2 cm

Dilated deep crypts and sessile architecture

J.G., 66 y/o woman, right colon
Polyp #5, 2.0 cm

Horizontal spread mimicking a viking ship
Deep crypt branching

“Hyperplastic Polyposis”
At least 5 histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which 2 are >10 mm in diameter, or
Any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis, or
> 30 hyperplastic polyps of any size but distributed throughout the colon.
What is the difference between a sessile serrated adenoma and a traditional serrated adenoma?

SSA V TSA

- Looks like HP
- Lacks conventional dysplasia

- Has pink cytoplasm and serration
- Has “pencillate” nuclei like conventional adenomas

Traditional Serrated Adenoma
Some authors have noted a characteristic architecture for traditional serrated adenoma ("ectopic crypt formation") and more features to help in DDX.


SSA = sessile serrated adenoma
TSA = Traditional serrated adenoma
CAD = Conventional adenoma
LOSO = loss of surface orientation

Sessile serrated adenoma — one can make a line from the lumen to the muscularis mucosae.

Hyperplastic polyp — one can make a line from the lumen to the muscularis mucosae.
Mixed Polyps

- We know that “mixed” polyps are simply sessile serrated adenomas that are progressing
Transition to Dysplastic Mucosa; “mixed polyp”
Serrated Polyps

- Hyperplastic polyp (>75%)
- Sessile serrated adenoma/polyp (15-25%)
- (Traditional) serrated adenoma (<10%)
- (Ad)Mixed polyp
- Sessile serrated adenoma/polyp with dysplasia
- Hyperplastic polyposis
- Serrated polyposis

WHO 2010
<table>
<thead>
<tr>
<th>Type</th>
<th>Synonym</th>
<th>Morphology</th>
<th>Microvesicular (MVHP)</th>
<th>Goblet cell (GCHP)</th>
<th>Mucin-poor (MPHP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 cm width, sharply defined</td>
<td>Commonest HP</td>
<td>Second common</td>
<td>Very rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prominent villosity</td>
<td>Entire colon</td>
<td>Left colon</td>
<td>&quot;Serration&quot; prominent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Location of villosity</td>
<td>Hyperplastic goblet cells</td>
<td>&quot;Serration&quot; subtle</td>
<td>Nuclear atypia present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presence of crypts</td>
<td>&quot;Serration&quot; prominent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not used in routine
No clinical significance

WHO 2010
Dealing with These SSA/SSPs

• How common are they?
• How often do they progress to cancer?
• What should we all be doing about them?

How Common?

• 2006 figure from Australia – 9% [Gastroenterology 2006; 131: 1400-1407]; endoscopists and pathologists were “in the know”

Cancer Progression Rate?

• Anecdotally a few per cent – Published estimate of 1/25 of such polyps of R colon
• In one small series of patients with hyperplastic polyposis, 7/12 developed cancers [a bit less than in adenomatous polyposis but these patients have far fewer polyps than those with FAP]
Cancer Risk and Rate of Growth

- 5 cancers in follow-up
  - 2/38 (5%) sessile serrated adenomas
  - 1/119 (0.8%) tubular adenomas
    - Statistically significant higher risk
  - 2/17 (12%) TVA

- Rate of growth (two endoscopies, divided size of polyp by time between two endoscopies)
  - HP (42): 1.36 mm/yr
  - SSA (26): 3.76 mm/yr
  - TA (50): 2.79 mm/yr


What Should We Do?

- At this point we are relying on common sense:
- Pathologists and endoscopists need to learn to better recognize this group of polyps
- They should be completely excised when possible
..in the future…

- Pathologists and endoscopists will learn to better recognize this group of polyps - New endoscopic techniques
- Consensus criteria will improve & standardize pathologic diagnosis
- Molecular data will become reliable
- Follow up data will provide information for better guidelines

Real life!

- All polyps should be excised (except <5mm, distal, multiple HPs)
- >1cm polyps should be completely excised
- Few small polyps - 5 year interval
- Large polyps - 3 year interval
- Dysplastic SSA/P control in 1 year, then 3 year interval

WHO 2010

Cancer Stats Estimates for Colorectal Cancer [Jemal]
Conclusion

- Basic tenets concerning colorectal polyps have exploded in the past few years.
- As we continue to adjust our practice to new information, we will be better able to serve our patients.