Prevention and Health Promotion Administration
Center for Cancer Prevention and Control
Cigarette Restitution Fund Program

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UNIVERSITY of MARYLAND

Serrated Polyps of the Colorectum

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- No disclosures.

Overview

- Polyp Types
- Clinical Features of Serrated Polyps
- Molecular Features of Serrated Polyps
- Problems with Serrated Polyps
- Follow-Up of Serrated Polyps

Colon Polyp Screening

- Cancer detection / prevention

Colon Polyp Screening

- Cancer detection / prevention
- Removal of precursor lesions (polyps)
- Pathologic identification of polyps
  - Allows risk stratification/appropriate follow-up

Polyps

- Masses of tissue projecting from the normal surface

- Mesenchymal polyps (lipomas, smooth muscle tumors, etc.)
- Lymphoid tissue
- Pseudopolyps

- Epithelial Polyps- overgrowth of epithelium

Normal Colon: Histology

- Straight, narrow crypts
- Small nuclei, at base of cell
- ‘Moderate’ amount of mucin

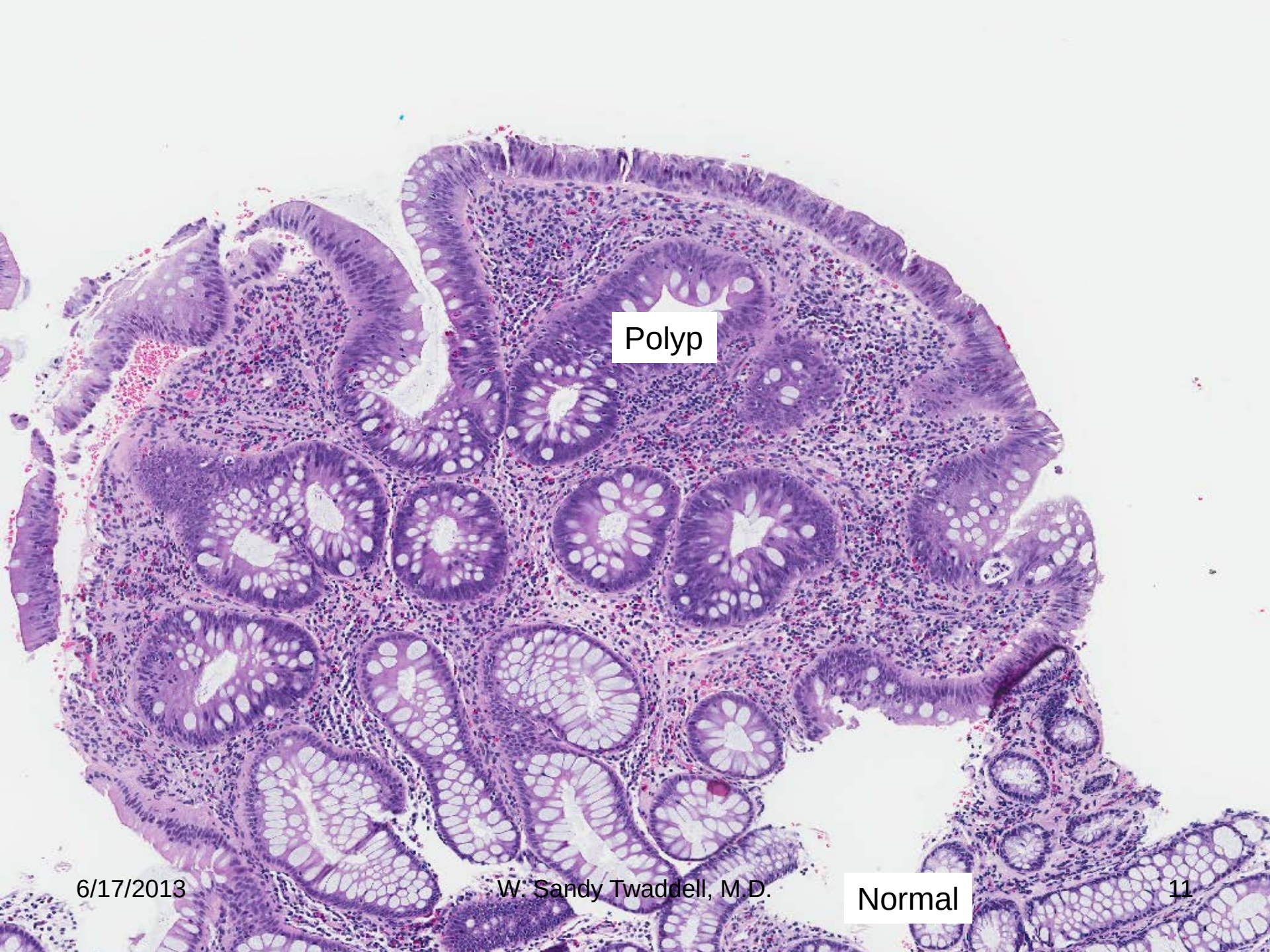
Normal

Epithelial Polyps: Histologic Findings

- Bigger nuclei, ‘picket fence’ or ‘cigar-shaped’
- Decreased mucin

  or

- Larger crypts with epithelial overgrowth extending into lumen → star-shaped or serrated lumens
- Increased mucin
- Small nuclei


Polyp
Normal

All polyp; no normal

Polyp Types: Then

- Adenomatous: less mucin, big nuclei
  - Tubular adenoma
  - Villous adenoma

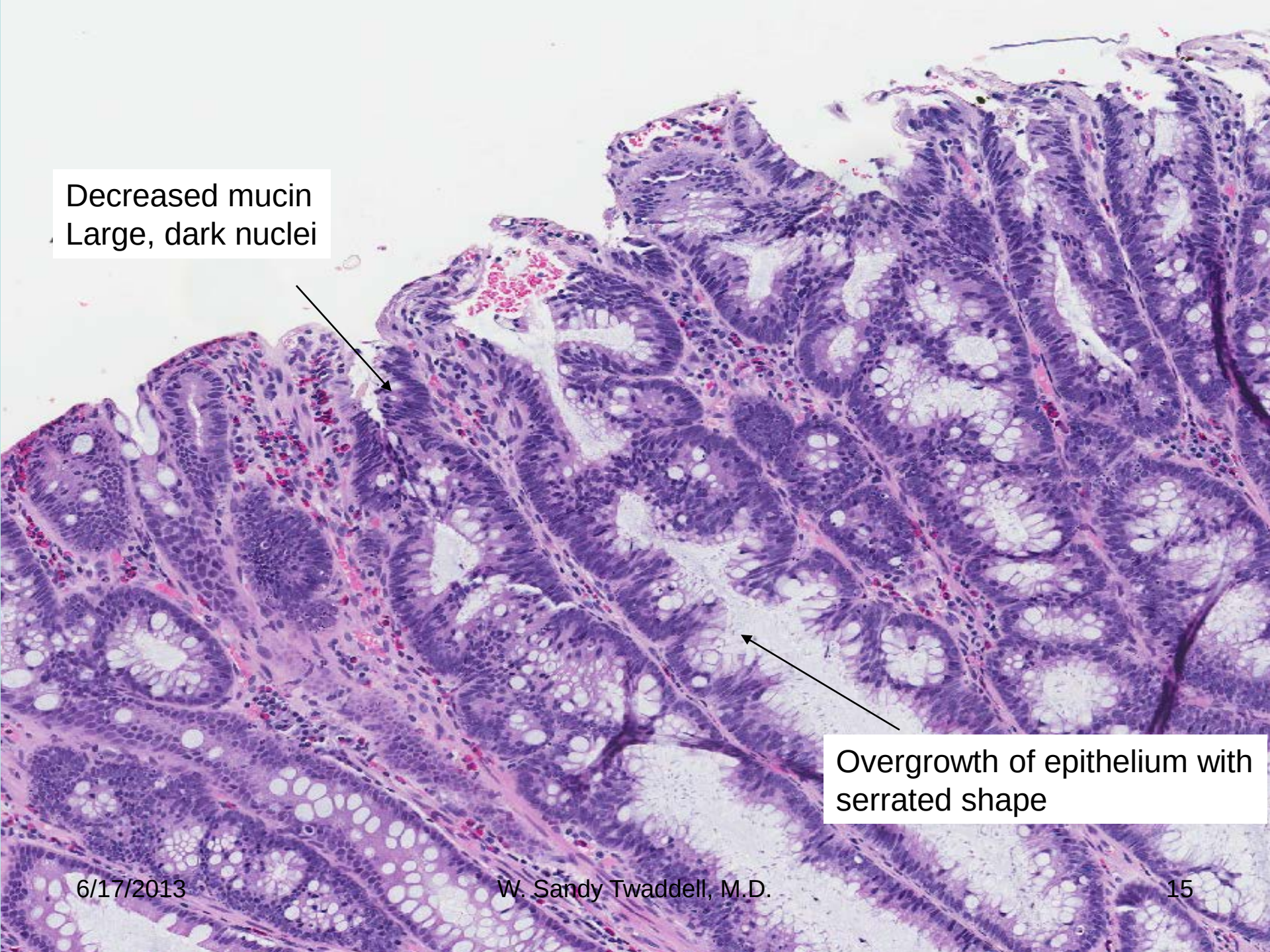
- Hyperplastic Polyp:

  increased growth, mucin; stellate/serrated lumens

Serrated Polyps

- Traditionally all serrated polyps were defined as hyperplastic polyps, dismissed as benign

- Increasing recognition of some polyps with ‘serrated’ look, with associated adenomatous features, that were associated with malignancy


Decreased mucin
Large, dark nuclei
Overgrowth of epithelium with serrated shape

Polyp Types: Then

- Adenomatous: less mucin, big nuclei
  - Tubular adenoma
  - Villous adenoma

- Serrated adenoma less mucin, big nuclei; serrated

- Hyperplastic Polyp

  increased growth, mucin; stellate/serrated lumens

Sessile Serrated Polyps

- Little change in nomenclature / categorization for ~ 10 years
- Starting around 2000, rapidly increasing interest in subtype of serrated polyps
  - Superficially resemble hyperplastic polyps (mucin-rich, without ‘adenomatous’ features) but otherwise atypical for hyperplastic polyps (size, location, etc).
  - Many different names applied to these:

- hyperplastic polyposis
- giant hyperplastic polyp
- giant hyperplastic polyposis
- large hyperplastic polyps
- hyperplastic-adenomatous polyposis syndrome
- mixed epithelial polyp
- mixed hyperplastic/adenomatous polyp
- serrated adenoma

Sessile Serrated Polyps

- Differences in morphology substantiated by differences in behavior and molecular features
  - Recognition based on molecular data that most of these represent a distinct neoplastic pathway
- (Gradual) reorganization of nomenclature to account for this

Polyp Types: Now

- Adenomatous
  - Tubular adenoma
  - Villous adenoma

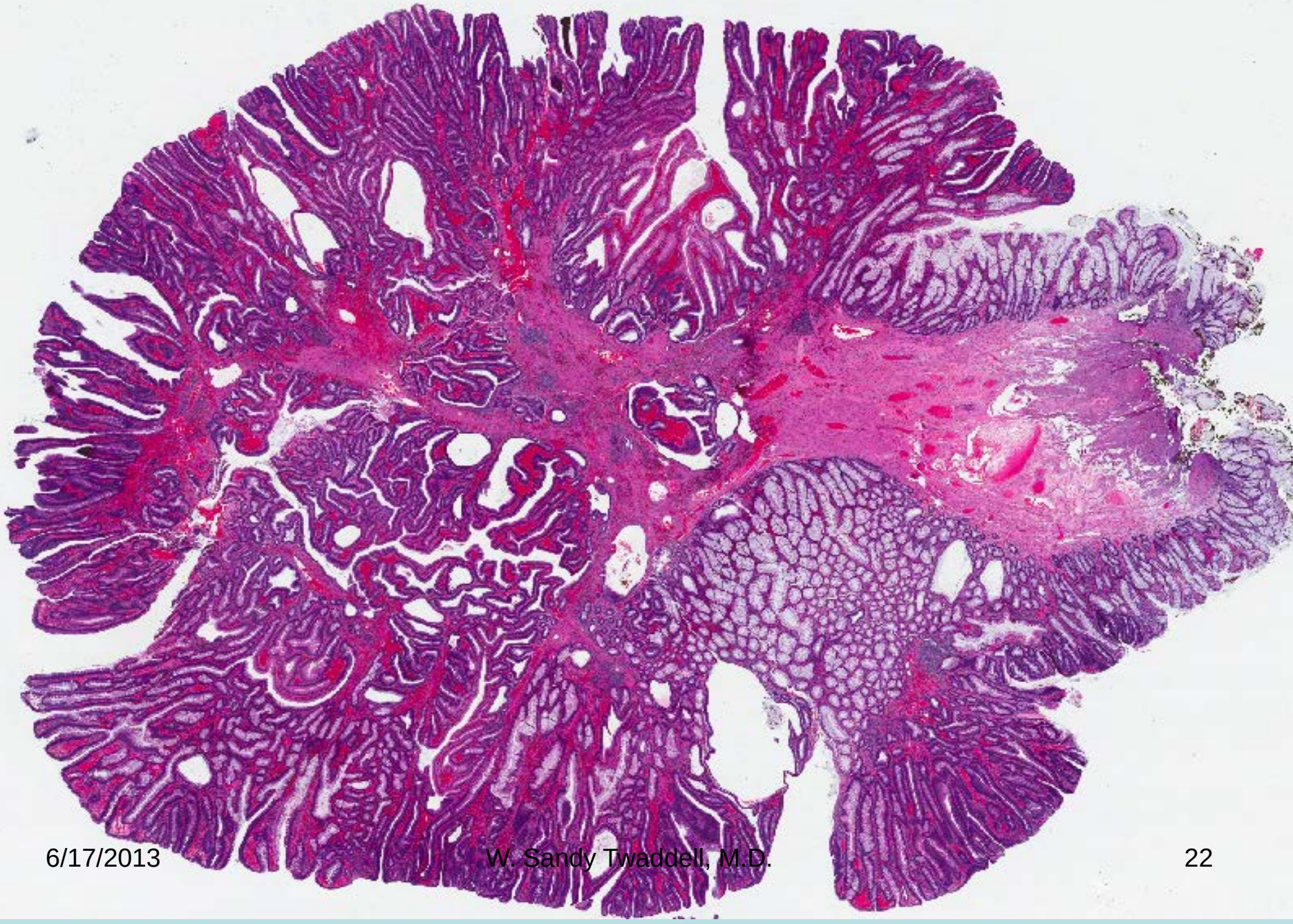
Polyp Types: Now

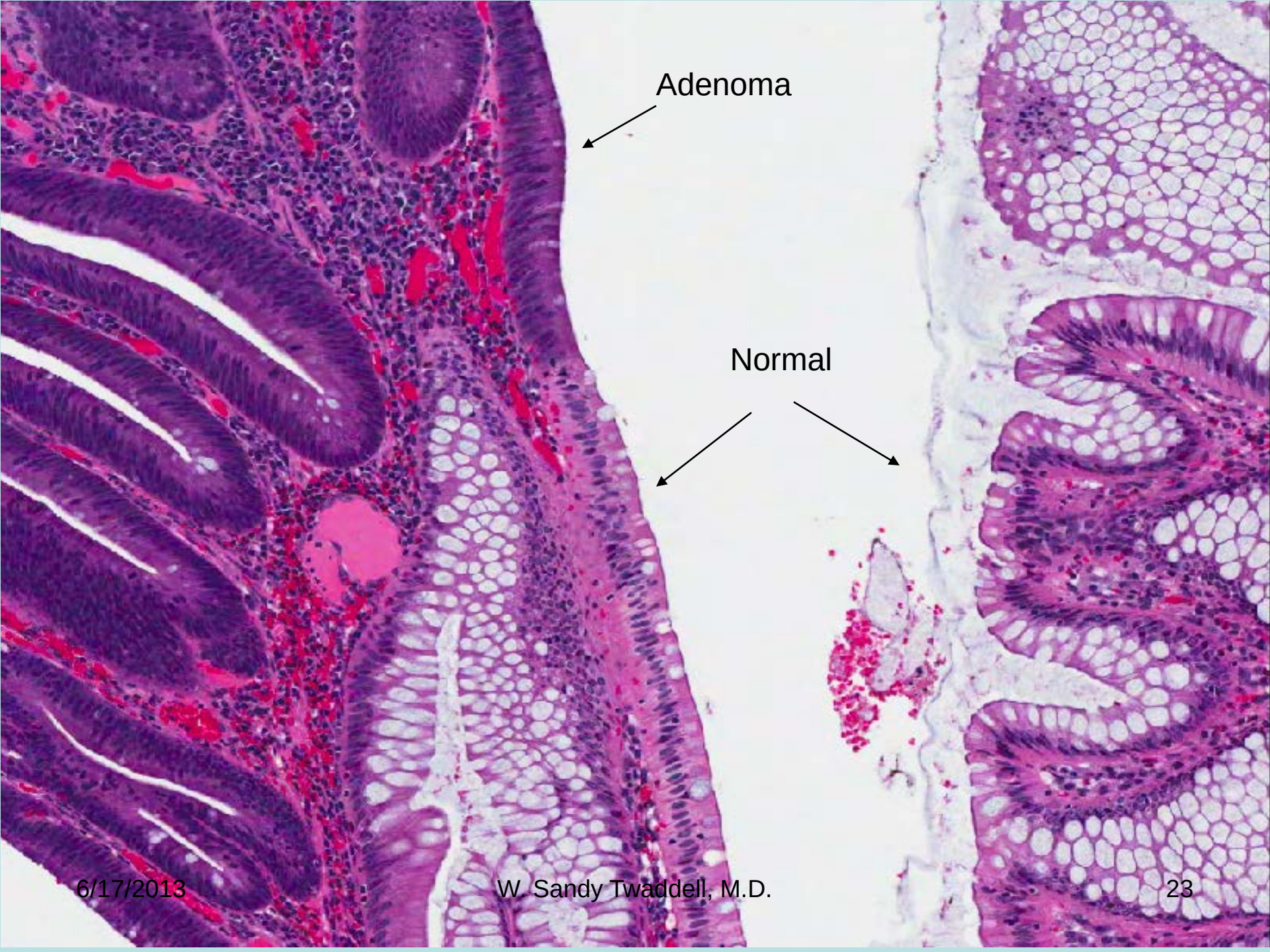
- Adenomatous
  - Tubular adenoma
  - Villous adenoma
- Serrated
  - Hyperplastic
  - Sessile serrated adenoma/polyp
  - Serrated adenoma (traditional)

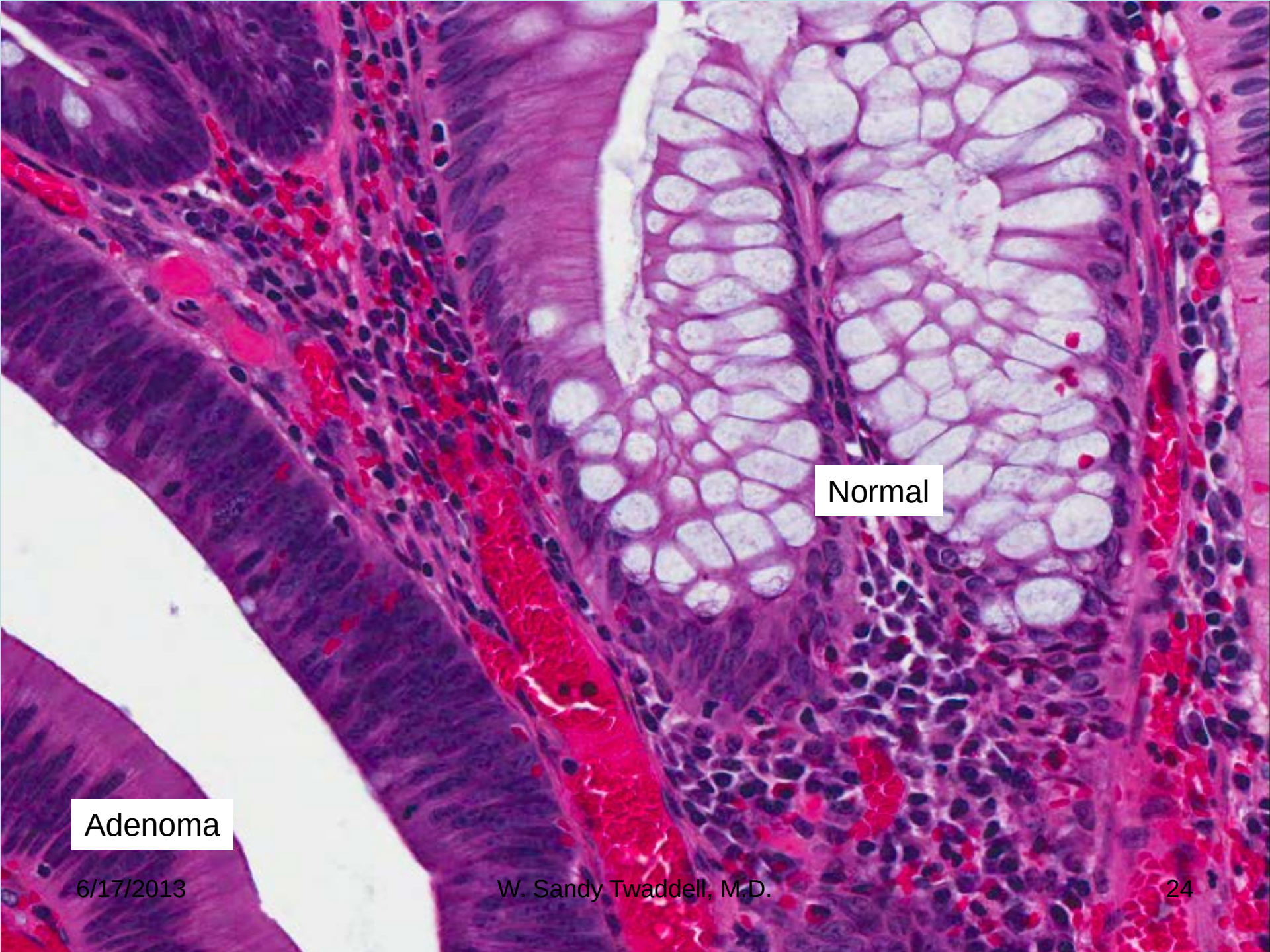
Adenomatous Polyps

- Traditionally, the polyp type that we worry about

- Marked increase in frequency with increasing age
- Neoplastic (chromosomal instability) with malignant potential
- Villous (if mostly growing out) or tubular (if mostly growing in)




Adenoma
Normal


Normal
Adenoma

Serrated Polyps

- Hyperplastic polyp
- Sessile serrated adenoma /
  sessile serrated polyp
- Serrated adenoma /
  traditional serrated adenoma

Hyperplastic Polyps (HPs)

- Most common serrated subtype (70-95%)
- Predominantly left-sided
- Usually small (< 5 mm)

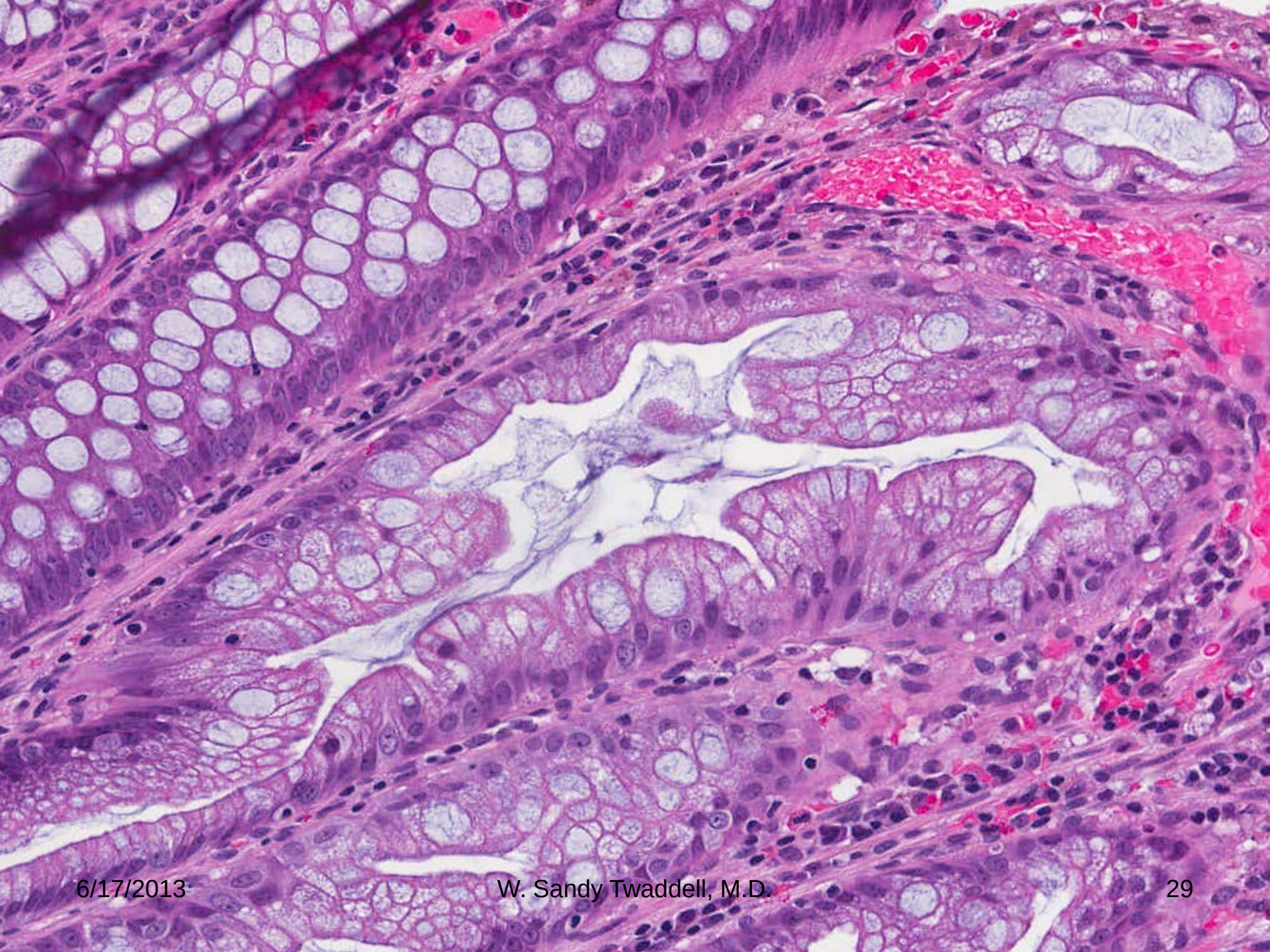
- Benign
  - May contribute to serrated polyposis syndrome

HP Appearance

- Straight, simple, symmetric crypts
  - No branching
- Wider and more serrated at the top
- Bland cytology, i.e., individual cells look basically normal
- Several different subtypes
  - No clear clinical difference between subtypes

Hyperplastic Polyp

Normal



Sessile Serrated Adenoma / Sessile Serrated Polyp

- Relatively new term (2003)
  - Concept is somewhat older
  - Slow and somewhat uneasy adoption into general pathology practice
- Malignant potential
- Nomenclature: ‘adenoma’ vs ‘polyp’
  - Use of both terms: ‘sessile serrated adenoma/polyp’

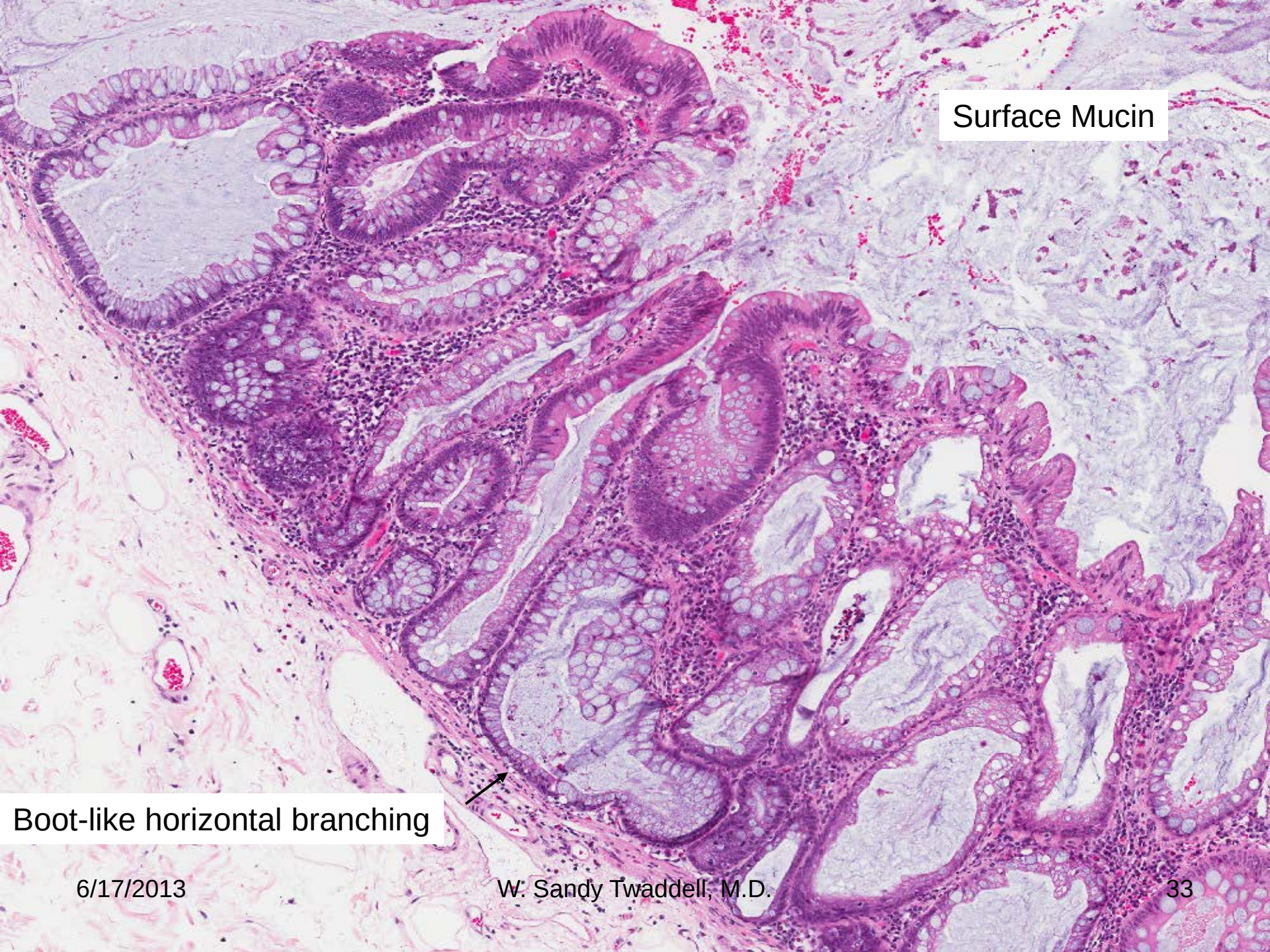
SSP Appearance

- Serrated, mucin-rich appearance
  - May have mucin coating the surface
- Distorted architecture
  - Branching and dilation, ‘boot-like’ shape at base
- Increased maturation at base
- Increased proliferation

- May have increased cellular atypia (low- or high-grade dysplasia)

- May have areas that look like HP


Branching/lateral extension


Surface Mucin
Boot-like horizontal branching

Sessile Serrated Polyp

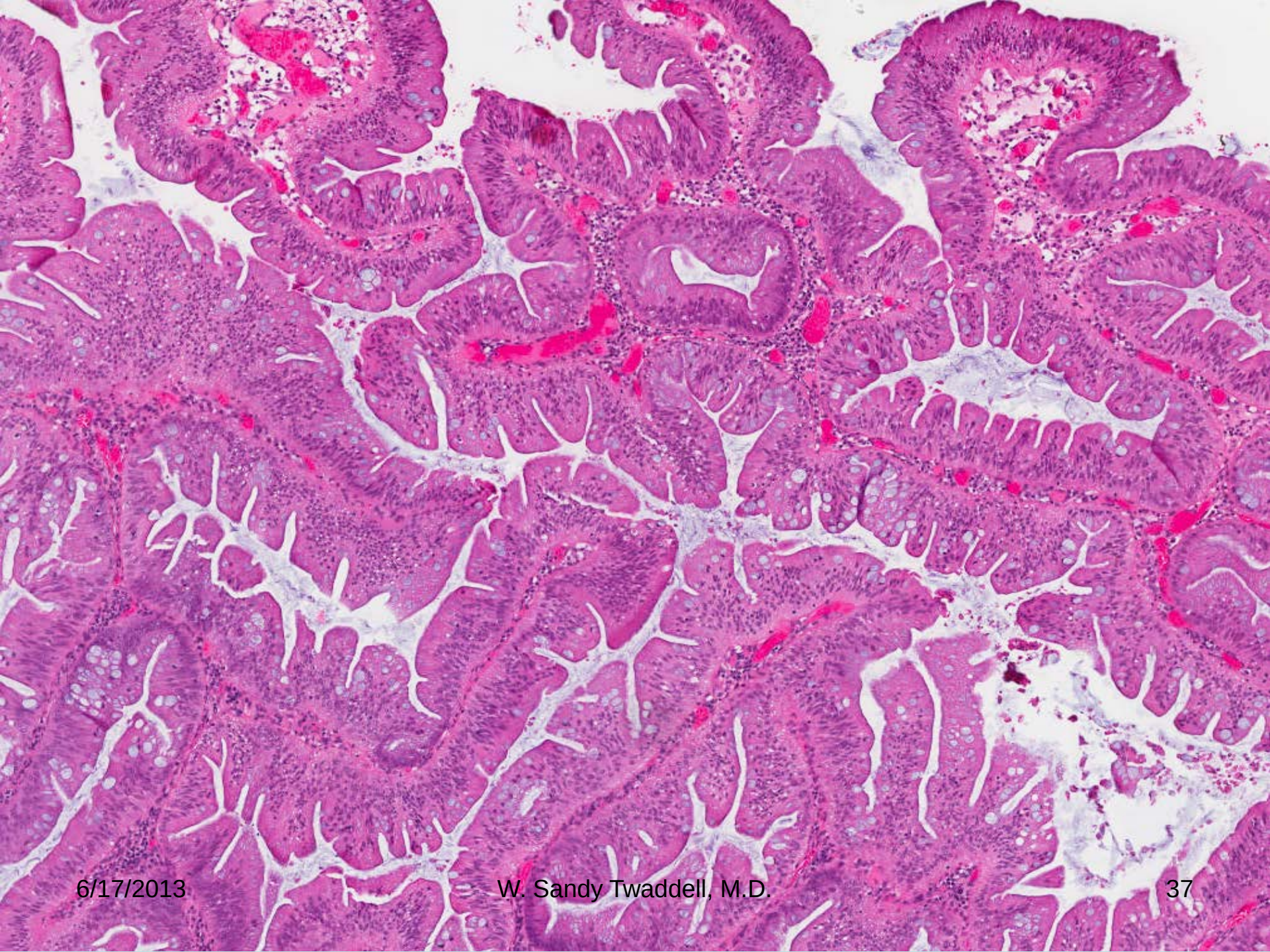
- How many ‘boot-like’ crypts?
  - WHO: 3
  - Consensus statement: 1

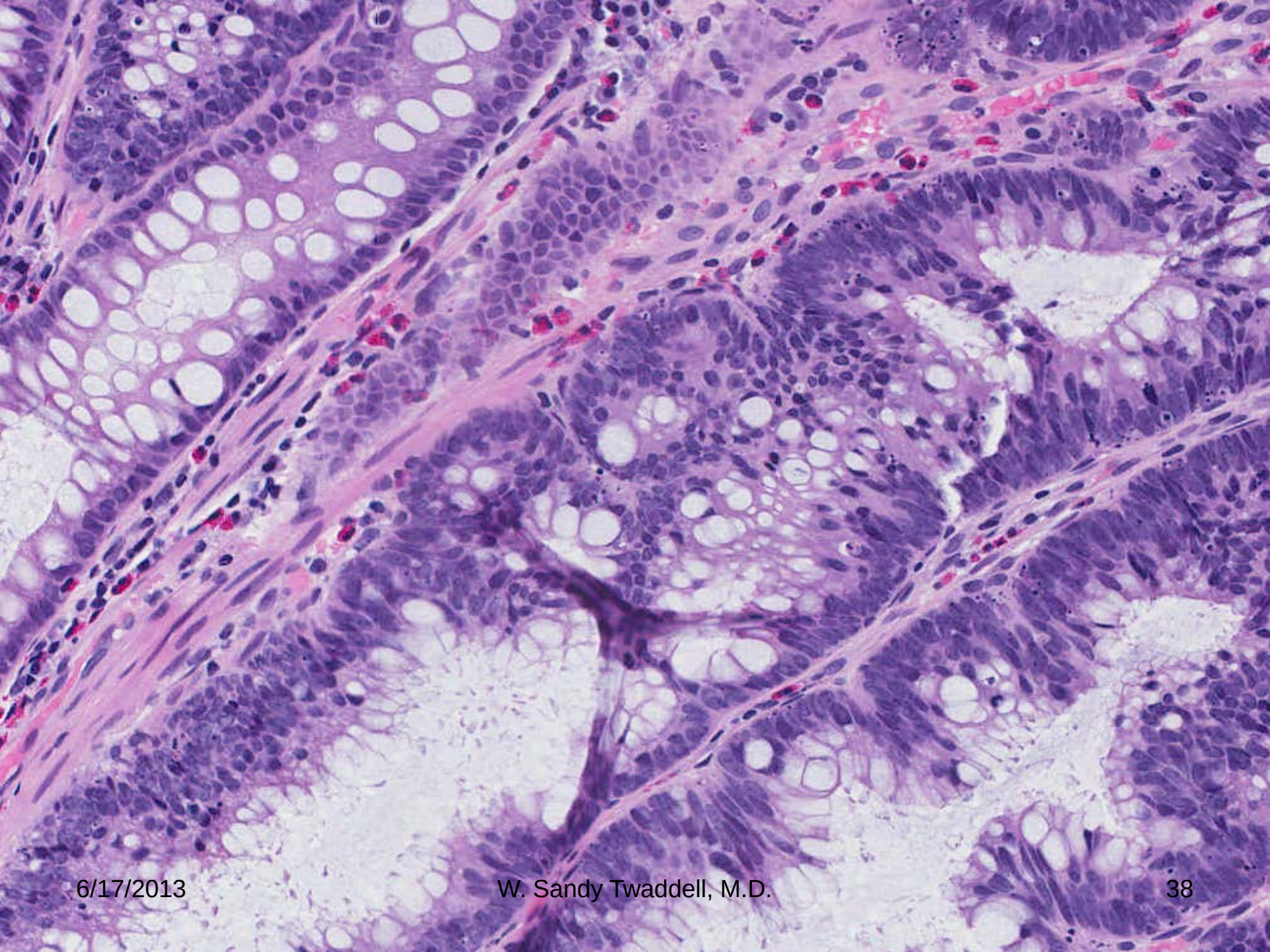
Serrated Adenoma / Traditional Serrated Adenoma

- Least common type
- Not well defined
  - Studies probably contaminated with other polyp types
- Malignant potential

TSA Apperance

- Stellate/serrated appearance
  - Decreased mucin production
- Variably dysplastic epithelium (low, high)





Unclassifiable Serrated Lesions

- Reasons you may get this diagnosis:
  - Overlapping histologic features
  - Technical problems with specimen or processing

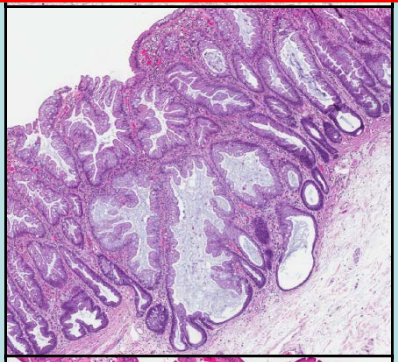
Conventional Adenoma with Serrated Features

- Usually occur in patients with other serrated lesions
- Substantial proportion share molecular features with serrated polyps

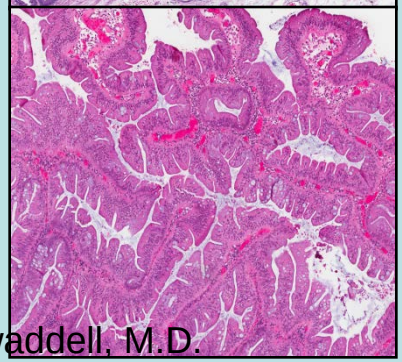
Serrated Polyp Types: Review

- HP - prototype
  - Common, distal
  - Small
  - Benign

- SSP – **branching crypts**
  - Common, proximal
  - Large
  - Malignant potential



- SA – **decreased mucin**
  - Rare, proximal
  - Large
  - Malignant potential



Epidemiology of Serrated Lesions

- Increase with increasing age

- Location:
  - More numerous in distal colon
  - More significant in proximal colon

Risk Factors for Serrated Lesions

- Distal (relatively less important, clinically)
  - Increased risk: cigarette smoking
  - Decreased risk: folate, exercise
  - Unclear: EtOH, fiber, NSAID, family CRC history, BMI
- Proximal (less data)
  - Increased risk: cigarette smoking

Molecular Features of Serrated Lesions

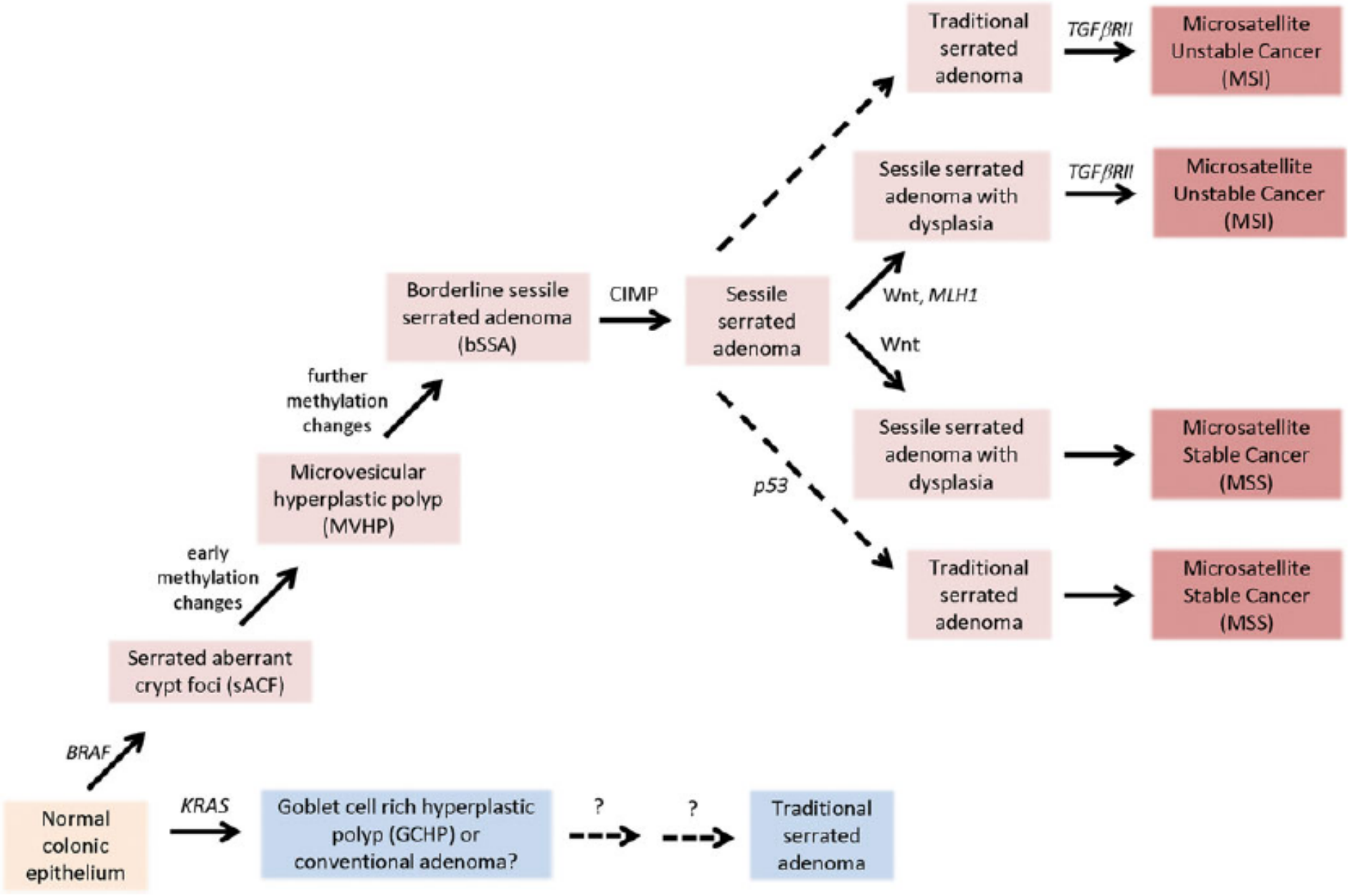
- Molecular Pathways of Carcinogenesis
  - Chromosomal instability (traditional, most adenomas)
  - CpG island methylator phenotype (CIMP)
  - Mismatch repair defects (MSI)
- SSP progression involves several of these

MAPK Pathway Alteration

- BRAF mutations as early event
  - ~50-70% of serrated polyps
- KRAS mutations less common

CIMP

- CIMP-high (methylation of an extensive set of genes)
  - Possible epigenetic silencing of MLH1 → MSI
- Present in some HPs, most SSPs
  - SAs more heterogeneous; possibly not a pure group


Traditional serrated adenoma
TGFβRII
Microsatellite Unstable Cancer (MSI)
Sessile serrated adenoma with dysplasia
TGFβRII
Microsatellite Unstable Cancer (MSI)
Borderline sessile serrated adenoma (bSSA)
CIMP
Sessile serrated adenoma
Wnt, MLH1
Wnt
further methylation changes
Microvesicular hyperplastic polyp (MVHP)
p53
Sessile serrated adenoma with dysplasia
Microsatellite Stable Cancer (MSS)
early methylation changes
Traditional serrated adenoma
Microsatellite Stable Cancer (MSS)
Serrated aberrant crypt foci (sACF)
BRAF
Normal colonic epithelium
KRAS
Goblet cell rich hyperplastic polyp (GCHP) or conventional adenoma?
?
?
Traditional serrated adenoma

Rosty *et al*

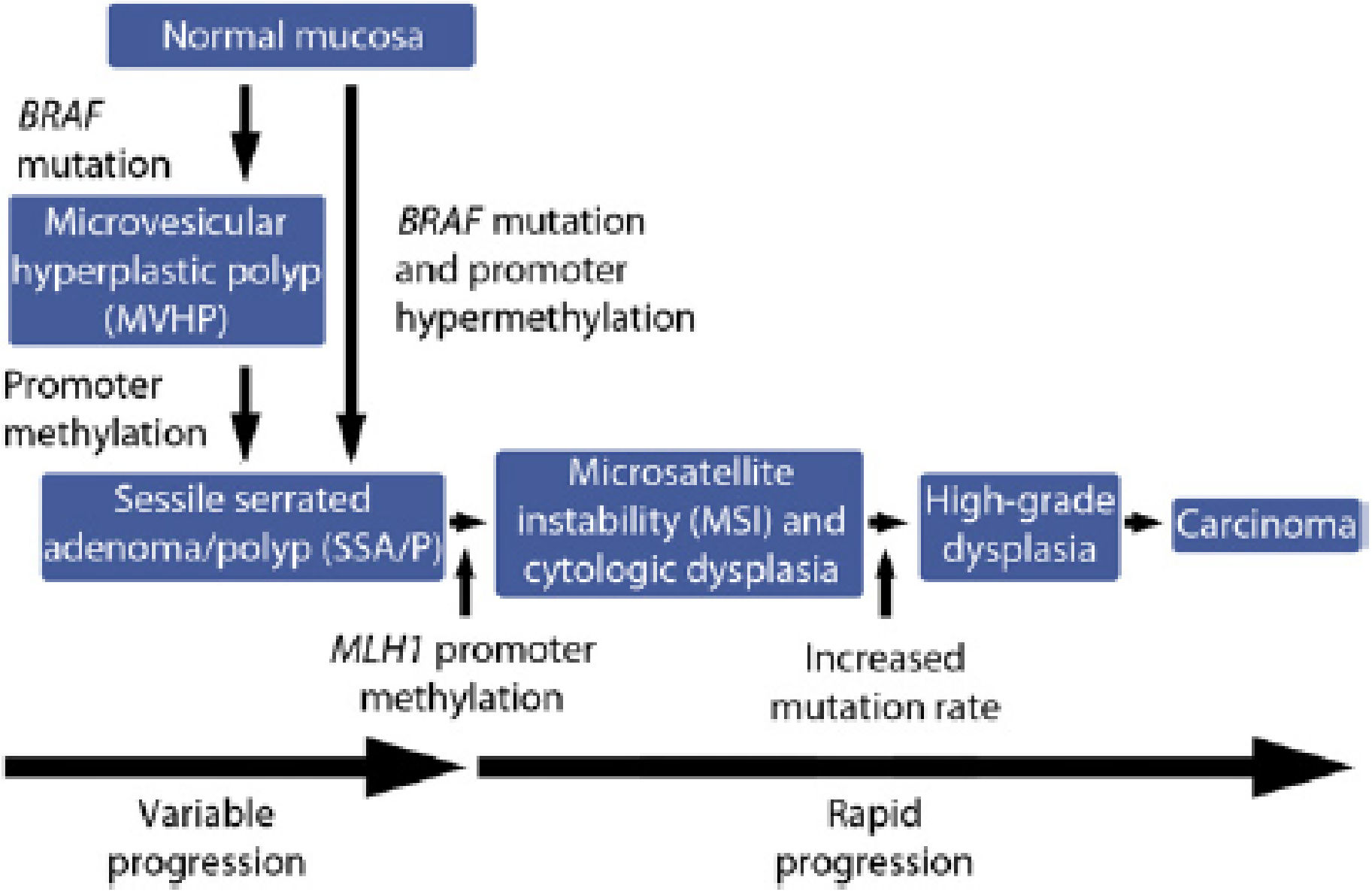
Proposed Serrated Lesion Progression

SSP → dysplasia → carcinoma

- Although HPs share some molecular features with SSP, no evidence that they're premalignant
  - CIMP cancer risk increases progressively towards the proximal colon; HPs most common in the distal colon

SSP → CA

Histology	**Mean Age**
SSP	61
SSP with low-grade dysplasia	66
SSP with high-grade dysplasia	72
SSP with carcinoma	76



Limketkai *et al*

Serrated Polyposis Syndrome / Hyperplastic Polyposis Syndrome

- Predisposition to serrated polyps
- Relatively younger age of onset
- Family history of serrated polyps or colon cancer
  - Many cases are sporadic

SPS: Definition

1) At least 5 serrated polyps proximal to the sigmoid colon, with at least 2 > 10mm, *or*
2) Any serrated polyps proximal to the sigmoid colon, in someone with a 1st degree relative with SPS, *or*
3) More than 20 serrated polyps, of any size, in any site in the colon

Fundamentally arbitrary definition

SPS: Significance

- Increased risk of colon cancer
  - Uncertain degree
- If undergoing resection for carcinoma, also resect segments with large polyps
- Annual colonoscopy with removal of proximal polyps
- Screening for 1st-degree relatives starting at age 40
- No obvious risk of extracolonic malignancy

Problems With Serrated Lesions

- Diagnostic
  - Recognition of serrated lesion
  - HP versus Everything Else
  - Use of appropriate nomenclature

- Management
  - Diagnostic variability
  - Guidelines?

Diagnostic Problems

1. Lack of clear nomenclature; inconsistent application of established nomenclature
   - What is it?

2. Lack of specific criteria
   - How do we know what it is?

3. Pathologist disagreement
   - Knowledge of nomenclature/criteria
   - Pathologists may just disagree anyway

1. Nomenclature

- Should be less of a problem, as concept of HPs / SSPs / TSAs is fairly well-established by now
  - Education

- Can’t tell / want to play it safe
  - May be related to lack of clear diagnostic criteria
  - Sign-out as ‘serrated polyp’ or ‘serrated lesion’
    - Because some are benign, some have malignant potential: not really a useful diagnosis

2. Diagnostic Criteria

- Good news:
  - Some guidelines emerging

- Bad news:
  - Guidelines are recent; will probably take a while to catch on
  - Some entities still not well defined (TSA)
  - Data lacking for many of these decisions
    - Tendency to ‘play it safe’ and overdiagnose to ensure adequate follow-up

SSP vs HP

- Biggest problem (common polyps, with very different follow-up implications)

- Recommendation (as of 6/2012):

  Even one distorted / ‘boot-like’ crypt is sufficient for SSP

3. Pathologist Disagreement

- Historically, a lot of interobserver variability
  - Improved when pathologists given clear rules

- Should improve as problems with nomenclature and diagnostic criteria are resolved

Management Problems

1. Diagnostic variability/vagueness
   - Should (hopefully) continue to improve in the future
2. Lack of clear guidelines
3. Clinician familiarity with diagnosis

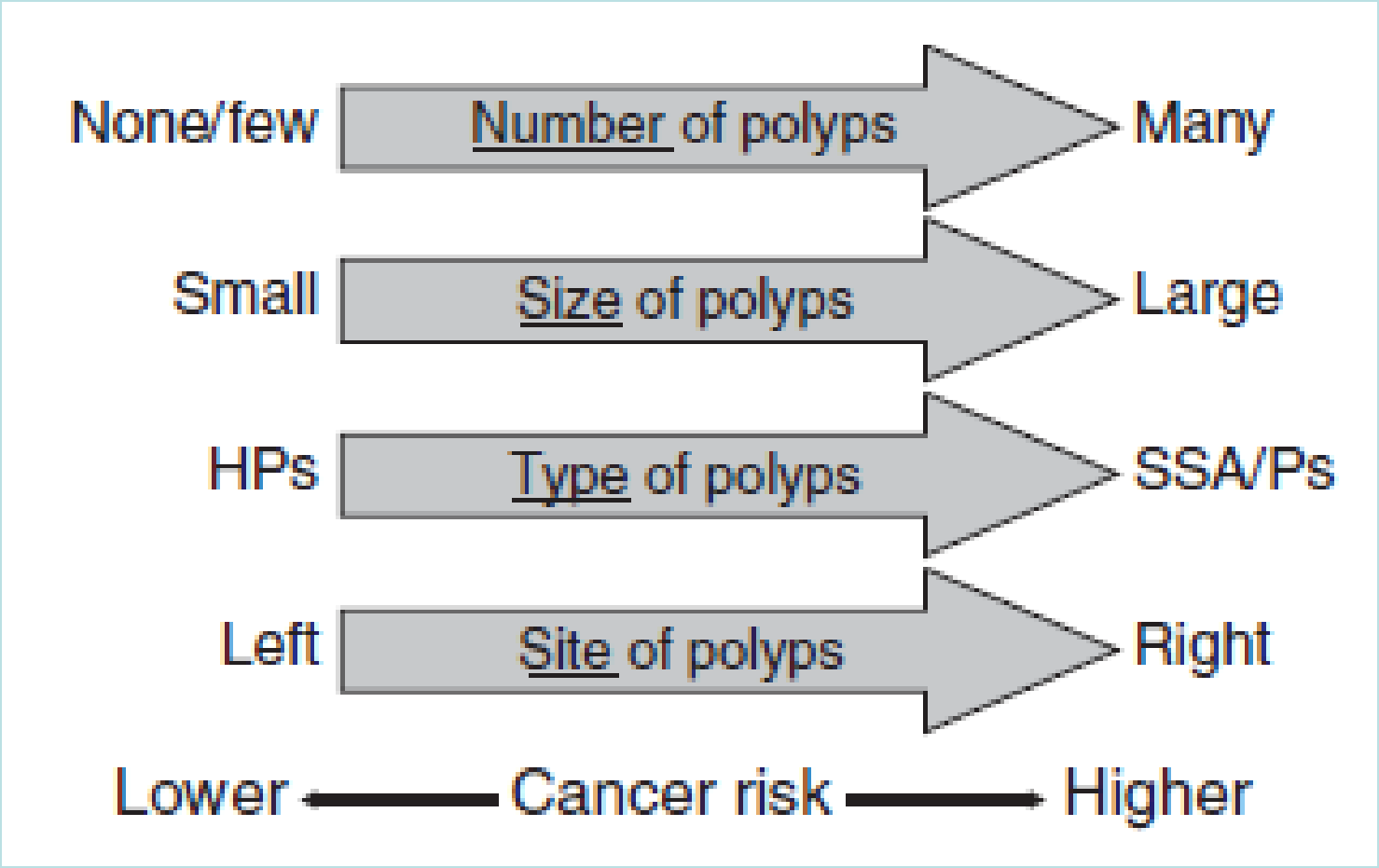
Follow-Up: Guidelines

- Recent consensus statement (Rex *et al*, Am J Gastroenterol, 2012)

- Important considerations include:
  - Number
  - Location
  - Size
  - Histologic subtype

- Not a lot of evidence regarding natural history to guide follow-up guidelines

Follow-Up: Basic Principles



From Rex *et al*, Am J Gastroenterol, 2012

Follow-Up: HP

Histology	Size	Number	Location	Interval in years
HP	<10 mm	Any number[b]	Rectosigmoid	10[c]
HP	≤5 mm	≤3	Proximal to sigmoid	10
HP	Any	≥4	Proximal to sigmoid	5
HP	>5 mm	≥1	Proximal to sigmoid	5

Lesions diagnosed as HP larger than 1 cm should probably be considered as SSA/P

From Rex *et al*, Am J Gastroenterol, 2012

Follow-Up: SSP/SA

Histology	Size	Number	Location	Interval in years
SSA/P or TSA	<10 mm	<3	Any	5
SSA/P or TSA	≥10 mm	1	Any	3
SSA/P or TSA	<10 mm	≥3	Any	3
SSA/P	≥10 mm	≥2	Any	1–3[d]
SSA/P w/dysplasia	Any	Any		1–3[e]

From Rex *et al*, Am J Gastroenterol, 2012

Take Away

- Accurate characterization of the number, size and location of lesions is dependent on the endoscopist.

- Accurate characterization of histology is dependent on the pathologist.
  - Can be quite variable
  - Advent of clear-cut guidelines may help in the future

What Your Report Says
(And what to do about it)

- Hyperplastic polyp: Benign
  - However, look for size/number/location: may indicate closer follow-up, worth commenting on
- SSA/SSP: Malignant potential, closer follow-up
- TSA: Malignant potential, closer follow-up
- 'Serrated lesion, unclassifiable':
  - Give the reason that it's unclassiiable
  - Presence/absence of dysplasia should be stated
  - No guidelines for follow-up
- Conventional adenoma with serrated features
  - No specific guidelines for follow-up

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THANK YOU!

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For questions please contact Kelly Kesler, M.S., C.H.E.S. at (410) 767-0786

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