Henry Moon was one of the giants in academic pathology during my early years. He and my boss, Jim French were cronies going back to WWII.

I never met him, but I heard a lot about him, all of it good. Thanks to Linda and her gang for giving me this honor of delivering the Moon Lecture.

Controversial stuff that occurs slightly above, within or slightly below the gastroesophageal junction, including Barrett’s mucosa: What role do we pathologists play?

We fuss a lot over goblet cells & cancer in and around the GE junction, but do they deserve all the fuss?
Pretty small considering the size of everything around it!

Let’s start with 2 cases

#1: Dyspeptic adult woman not responding to medication (PPIs) has upper endoscopy. The endoscopist saw erythema at the gastroesophageal junction. Nothing else. The erythema was biopsied
Biopsies of erythema are among the least informative of all biopsies.

But we won’t discourage the GI people from biopsying erythema. We need the business!!

Biopsies of erythema account for about 7% of my income.

Chronic inflammation!
Plasma cells

Pancreatic acinar metaplasia (PAM)

Pancreatic acinar cells mixed with cardiac gland mucus cells

2

Don’t confuse these with real goblet cells

3 Huge pit cells: pseudogoblet cells

Don’t confuse these with real goblet cells
Summary
Endoscopic erythema at the GE Junction. No endoscopic Barrett’s mucosa

Squamous and columnar mucosae
The columnar mucosa has
  Inflammation: plasma cells
  Goblet cells...and mimics
  Pancreatic acinar cells in the cardiac glands

SO?

This is a common biopsy. It is annoying, because it does not have a standard name has a lot of features, but what do they all mean? I will deal with this. does not answer the clinical question: what caused dyspepsia?

Finally, way off at the edge of the biopsy
The evil, dreaded goblet cells!!
#2: Obese adult white male (the Barrett model)
Heartburn for 20 years, recently worse
Not responding to PPIs
GEJ tongues: “cannot tell if this is an exaggerated Z-line or short segment Barrett’s”
Bx taken of the tongues
Pathologist told (not asked) to R/O Barrett’s
(The true request was to R/I Barrett’s)

Summary
Endoscopic: changes that may be either an exaggerated Z-line (squamocolumnar junction) or short segment Barrett’s mucosa
Histologic:
- Columnar mucosa
- Inflammation
- Goblet cells.....and mimics

These 2 sets of biopsies around the gastroesophageal junction have

- Columnar mucosa
- Impressive chronic inflammation
- Goblet cells

SO?
There are 2 compelling reasons

First: Because it includes Barrett’s mucosa and the gastric cardia, both of which have cancer associations.

Everything interesting and contentious about the cardia and Barrett’s is driven by cancer risk because cancers in and around the GEJ are said to have been increasing at a great rate in western societies.

Otherwise, we wouldn’t care!
Adenocarcinomas at and around the Gastroesophageal Junction

Sometimes (often?) we cannot tell where the cancer is arising!

Distal Esophagus (Barrett’s)
Junctional NOS

Fundus
Cardia
Upper Body

Second:
The GE junction affects my standard of living much more than its size suggests it should!

Disclaimer:
About 10% of my income is derived from specimens taken from the GEJ and nearby.

Our clients, the gastroenterologists actually have to deal with 2 junctions.
**Junction #1**
The Squamocolumnar Junction (Z-line) an endoscopic (gross) visible line

Spechler SJ. Gastroenterol 117:218, 1999

**Junction #2**
The Gastroesophageal Junction: an endoscopic less obvious line.....

Defined somewhat arbitrarily, as the level of the most proximal extent of the gastric folds

Spechler SJ. Gastroenterol 117:218, 1999

Top of the proximal fold

Thus, the GE Junction

Also, the squamo-columnar junction (Z-line)

Top of the proximal fold

Thus, the GE Junction

Also, the squamo-columnar junction (Z-line)

Another definition of the GEJ is the point where the lumen flares
The Cardia

There are 2 cardias
1. The gross anatomic structure
2. The microscopic mucosa
   Of these, the important one is the microscopic mucosa

If we want to study the cardia, where should we find it?
The Gross Cardia

Where in the hell is it?

The AJCC gave it a site code: C16.0 which includes cardia and EG jct. Their definition of the cardia in 2010: “The proximal 5 cm of stomach”

Published Definitions of the Cardia:
seem to mix gross and microscopic

1. No size.
2. About 1 cm long
3. 1-2 cm long
4. Several cm long
5. 0.5 to 4 cm long

Published Definitions of the Cardia

6. Within 5 cm of EGJ
7. 1 cm proximal to 2 cm distal to the EGJ
8. Narrow zone between esophagus and stomach
9. A small ill-defined area, extending 1-3 cm from the GEJ

(Owens, Hist for Pathol, 2012)
Where is the cardia?

Somewhere around here

If you want to study the cardia, where do you take biopsies?

Across the normal squamo-columnar junction

Is cardiac mucosa normal?

Studies from U Southern California conclude that cardiac mucosa is abnormal and due to reflux, and that it is the precursor of Barrett's mucosa (Chandrasoma, et al, AJSP, 2000 to present)

Other studies indicate cardiac mucosa occurs in infants and children, suggesting that it is normal (Zhou, et al, Mod Pathol, 1999, Kilgore, et al, AJG, 2000)

Suggestions that it may be normal in some and abnormal in others
It doesn’t matter if cardiac mucosa is normal or abnormal. It exists, so we have to deal with it!

Cardiac mucosa is usually inflamed.

Carditis
Chronic: Plasma cells
Activity: PMNs

Cardiac intense inflammation
Oxyntic very mild inflammation
**Carditis**

**Definition:** microscopic inflammation in cardiac mucosa

Almost every cardiac mucosa has some

**Causes:** Currently an enigma
- H pylori? The intense active/chronic forms
- Acid Reflux? Data inconsistent
- Bile Reflux? One study from Leeds
- Unknown? Many ?most mild cases
- Multifactorial? Possibly

---

**Pancreatic Acinar Metaplasia**

- Is it a metaplasia, or is it congenital?
  - 16% peds cardiac bx
- Is it a disease, or is it normal?
  - Common in the cardia
  - 24% of 155 adult junction bxs
- So far: no significance

---

**Carditis: 2 types in Boston**

<table>
<thead>
<tr>
<th>Type</th>
<th>GERD sx</th>
<th>active esophagitis</th>
<th>H pylori gastritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>H pylori</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

**Results of analysis**

- **Overall**
  - PMNs: fewer, fewer, fewer
  - Plasma: more, more, more
  - Multilayered epithelium: yes, no, 7:3
  - M:F: 3:5+

**Goblet Cells in Cardiac Mucosa**

- Numerous studies
- Sites of biopsies vary
  - lower 2-3 cm of esophagus (as long as the SCJ is normal)
  - 2-3 cm below the GEJ
- Prevalence of goblet cells: 3% to 36%
- The M:F = 0.4:1 to 9:1

---

**How common is cardiac IM**

4 US centers, 940 adults 40 yrs and older who came for colonoscopy and agreed to have upper endoscopy.

122 (12.9%) cardiac goblet cells

associated with advancing age and +H pylori test


---

**Goblet Cells in Cardiac Mucosa**

195 patients, elective upper endoscopy
- no endoscopic Barrett’s
- magnification endoscopy with acetic acid spraying
- single targeted biopsy of specific mucosal types

86 (44%) had intestinal metaplasia (goblet cells)

- villiform pattern: 60%
- Cerebriform pattern: 96%

**Conclusion:** with this technique, cardiac goblet cells are very common

Guelrud, et, Am J Gastroenterol 97:584-9, 2002

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This is utter nonsense!
Goblet Cells in Cardiac Mucosa

Causes
- acid reflux
- bile reflux
- H pylori
- at least 2 of the above
- something else

Goblet Cells in Cardiac Mucosa

Significance:
We worry that they are markers of high cancer risk. There is no data that they are.

Cardiac IM called “histologic Barrett’s mucosa” in a German study
128 patients with 5 yr follow-up
33 (26%) developed endoscopic Barrett’s
Known length in 26 of the 33
12 pts: <1cm short
11 pts: 1 to <3cm segment
3 pts: ≥3cm (long segment)

No idea what this means for neoplastic risk

So whenever cardiac mucosa is biopsied, you get various combinations of...
#1: Dyspeptic adult woman not responding to medication (PPIs) has upper endoscopy. The endoscopist saw erythema at the GE junction. Nothing else. The erythema was biopsied. Look what we got:

Histologic features of cardia biopsies in volunteers
226 adults, mean age 45, 61% F, 49% Afr-Am
2 jumbo bx at or within 5mm of the SCJ (some may be too distal)
Cardia, defined simply as presence of mucus glands, found in 191 (85%)
Chronic carditis in 70%
Active carditis in 30%, all definitely or probably H pylori
Goblet cells in 15%; PAM in 13%
Possible Diagnoses

- chronic carditis ± PAM ± IM of unknown etiology
- or
- chronic carditis ± PAM ± IM due to _____ (if you really believe you know)
- or
- no significant abnormality (since everyone has some, who cares?)

What do I do every day?

Before deciding, I polled my gastroenterologist colleagues to see what they wanted.

I asked them if they wanted to know if there was carditis, PAM and/or IM, and if so, which item would change their management of the patient.

They said they did not care about any of these items except for IM, which might affect management in certain circumstances.

My diagnosis (they want this):

- Minute focus of IM at the GEJ

What should be the diagnosis in other institutions or practices?

This depends on what the GI colleagues want to know. The best way to find out is to ask them.

Then tell them what they want.
**Summary**

Cardias are small
Cardias are often biopsied, so we see stuff
Inflammation is almost universal
  The cause is unknown
Goblet cells are common
  The cause is unknown
Significance is minimal if that much
Pancreatic acinar cells are common
  The cause is unknown

Other than for cancer and dysplasia, almost everything else that we say about a cardia in our reports is meaningless!

Now that I have killed **cardiac mucosa**, what about the other part of this discussion, Barrett’s mucosa?

This summarizes our approach to Barrett’s mucosa, including the definition we use.
Barrett’s Esophagus: Definition

A change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus.

Barrett’s definition

A change in the distal esophageal epithelium of any length. It is an esophageal disease, not a GE junction disease!

Barrett’s definition

.....that can be recognized as columnar type mucosa at endoscopy (it is grossly, i.e., endoscopically abnormal.)

Tongues of pink mucosa

Barrett’s Esophagus: Definition

.....and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus. (IM means goblet cells.)
Goblet cells are irrefutable evidence of metaplasia. This definition also avoids dealing with cardiac mucosa in the distal esophagus.

The cancer rationale:

**Gastric** mucosa with one type of **intestinal metaplasia** has an **increased cancer risk**

Mucosa without IM has **no** increased cancer risk.

The cancer supposition:

**Esophageal** mucosa with that same type of **intestinal metaplasia** has an **increased cancer risk**

Mucosa without IM has **no** increased cancer risk.
2014 Diagnosis of mucosal biopsies at or slightly above the GEJ

**Histologic findings**

- No goblet cells
- Goblet cells

**Endoscopic**

- Tongues above the GEJ
- Z-line, no tongues
- Not certain if tongues
- No information

**Diagnosis**

- No goblet cells
- No Barrett's!!!!!

**Barrett’s**

- Goblet cells
- Tongues above the GEJ
- Z-line, no tongues
- Not certain if tongues
- No information

**Columnar Blues**

- These columnar cells with acid mucin are metaplastic cells, but they are not considered to be equal to goblet cells for diagnosis.
Barrett’s: other cell types
- Endocrine cells
- Paneth cells

Barrett’s mucosa is also commonly inflamed.
No one seems to care!
Probably they just blame reflux.

How does the mucosa turn from squamous to columnar?

Squamous (normal)  Columnar (Barrett’s)

Barrett’s mucosa: theoretical progression

- Injury: We assume that this is refluxate
- Inflammation: Mediators > cellular
- Metaplasia (Barrett’s)
- Dysplasia
- Carcinoma

Why metaplasia? Squamous epithelium heals perfectly well.

We know a lot about the molecular and genetic changes here
How does the mucosa turn from squamous to columnar?

Studies using cultures of esophageal squames or mucosa found that acid and/or bile salts up-regulate intestinal differentiation factors like CDX2 and CDX1, or up-regulate HB-EGF in lamina propria fibroblasts that promotes CDX2, or stimulate BMP4 in stromal cells that promotes columnar cell keratins.

In the laboratory, reflux type substances induce changes in esophageal squamous cells that might precede intestinal metaplasia.

We need to prove that these (or other) factors actually cause this metaplasia in vivo.
Columnar metaplasia may be an adaptation by the host to better withstand the chemical (acid and bile) injury.


Barrett’s Mucosa
Multilayered epithelium
the proposed origin in Boston

Barrett’s esophagus: putative precursors

Submucosal gland duct
Cardiac mucosa
Stem cells at squamous base

Barrett’s mucosa has been separated into two types, based on segment length:

- **Long segment (LSBE):** 3 cm or more
- **Short segment (SSBE):** less than 3 cm

A less well recognized segment length has been called “ultrashort segment” (USSBE).

The definitions are not uniform.
One definition uses less than 1 cm.
Unfortunately, goblet cells at the GEJ is also sometimes referred to as “ultrashort segment Barrett’s mucosa”

Short segment Barrett’s
- Definition: < 3 cm of columnar mucosa above the proximal gastric folds
- Over-diagnosed endoscopically: 3/4 in one study, but 3/8 in another
- May not be found on subsequent endoscopy

Looks like short segment Barrett’s mucosa with typical red tongues

The biopsy was not Barrett’s

The red is probably due to increase in superficial blood vessels

Endoscopic pseudoBarretts
1. Papillomatosis in squamous
2. Healing ulcer in squamous
3. Cardiac mucosa
4. Normal squamous mucosa
Barrett’s: squamous metaplasia (Pseudoregression)

Broad stretch

May be stimulated by PPIs: lead to decreased endoscopic length and hidden stuff

What is hiding below the squamous metaplasia?

- The Barrett’s only
- Dysplasia
- Carcinoma

Barrett’s mucosa is a high-risk cancer precursor, right?
So all this fuss is worthwhile, right?

Or is it?

We need to know 2 things

1. How common is Barretts?
2. What really is the cancer risk?
3 US studies: Prevalence of Barrett’s in Males Stratified by Age

<table>
<thead>
<tr>
<th>Author</th>
<th>#</th>
<th>Age</th>
<th>%Barr</th>
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<tbody>
<tr>
<td>Ward</td>
<td>161</td>
<td>65+</td>
<td>22</td>
</tr>
<tr>
<td>Gerson</td>
<td>110</td>
<td>50+</td>
<td>25</td>
</tr>
<tr>
<td>Rex</td>
<td>572</td>
<td>40+</td>
<td>8</td>
</tr>
</tbody>
</table>

How common is Barrett’s in Sweden?

1000 randomly selected people in 2 Swedish places underwent upper endoscopy. Mean age 53.5 yrs, 51% women

- 16 (only 1.6%) had Barrett’s, 5 long segment
- 400 had reflux sx: 2.3% had Barrett’s
- 600 had no reflux sx: 1.2% had Barrett’s
- 103 had endoscopic esophagitis: 2.6% had Barrett’s
- 897 had no endoscopic esophagitis: 1.4% had Barrett’s

Alcohol and smoking were independent risk factors


There seems to be a lot of Barrett’s mucosa in the USA in older men.

The Swedes have very little, but we don’t live there!

What really is the cancer risk?

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Location</th>
<th>#pts</th>
<th>Cancer incidence</th>
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<tbody>
<tr>
<td>Spechler</td>
<td>2011</td>
<td>USA</td>
<td>N/A</td>
<td>0.5%/yr estimate</td>
</tr>
<tr>
<td>Wani</td>
<td>2011</td>
<td>USA</td>
<td>1204</td>
<td>0.27%/yr</td>
</tr>
<tr>
<td>Bhat</td>
<td>2011</td>
<td>No Ire</td>
<td>8522</td>
<td>0.22%/yr***</td>
</tr>
<tr>
<td>Hvid-Jen</td>
<td>2012</td>
<td>Denmark</td>
<td>11028</td>
<td>0.12%/yr</td>
</tr>
</tbody>
</table>

***included both IM and non-IM, CA esoph and cardia
Summary
Barrett’s mucosa is common
Carcinomas developing after negative initial biopsies are rare
Surveillance is expensive. Time to personalize surveillance.

How about a controversy mixing cardiac and Barrett’s mucosae?

Normal Cardiac Mucosa
Clustered mucus glands

Cardiac Mucosa with a twist
pits and glands equal thickness
Esophageal submucosal gland duct
Proof of tubular esophageal location
2006 British Society of Gastroenterology guidelines for the diagnosis and management of Barrett’s oesophagus (BO)

BO is defined as an endoscopically apparent area above the OGJ that is suggestive of Barrett’s which is supported by the finding of columnar lined oesophagus on histology. .....IM...is not a requirement for diagnosis. (because sampling may miss IM)


....They suggest that IM not be required for the definition of BO.....
If these came from mucosae that looked like endoscopic Barrett’s

Then these would be Barrett’s in the UK

#2: Obese adult male
Heartburn for 20 years, recently worse
Not responding to PPIs
GEJ tongues: “cannot tell if this is an exaggerated Z-line or short segment Barrett’s”
Bx taken of the tongues
Pathologist told (not asked) to R/O Barrett’s
(The true request was to R/I Barrett’s)

Diagnosis:
Cardio-esophageal junction, biopsy:
Columnar mucosa with goblet cells
Maybe add: either in the cardia or in short segment Barrett’s mucosa.

Comment:
If you can’t tell it is Barrett’s, neither can I!
(with a reference to Wang and Sampliner or Spechler or Fitzgerald, if that seems necessary)

Even in the UK this is not Barrett’s because of the endoscopic uncertainty
Some people in the US and in a few other places want us to adopt the British definition for Barrett’s that doesn’t require goblet cells.

They have some data to support this

3 studies:
cardiac mucosa without IM in the distal esophagus had **CDX2**, an intestinal differentiation marker, in some, but not all cases.

Groisman, et al, Mod Pathol, 17:1282, 2004

A study of endoscopically confirmed columnar epithelium in the distal esophagus by image analysis: mucosa with IM and without (cardiac type) had similar DNA content changes.

Stomach        No IM    IM
One study from Germany: 70% of 141 small (>2 cm) distal esophageal cancers treated by EMR were surrounded by cardiac mucosa, not mucosa with goblet cells.

No IM anywhere in over half of the EMR specimens

**Conclusion:** no support for the view that Barrett adenocarcinoma is nearly always accompanied and preceded by IM.


In contrast, another study from U of Southern California of esophageal, EGJ and cardiac carcinomas:

residual IM was found next to

- 52% of 33 tumors >4cm
- 76% of 36 tumors <4cm
- 100% of 8 tumors ≤1cm

92% of 26 tumors confined to the wall

Residual IM was related to tumor size.


Problems with these data: they are all retrospective

We want to know if non-IM mucosa needs surveillance. Specifically, does it have the same cancer risk as does IM mucosa

AGA Institute Medical Position Panel

Definition of Barrett's Esophagus

"the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium.......

Presently, intestinal metaplasia is required for the diagnosis..... because intestinal metaplasia is the only type of esophageal columnar epithelium that clearly predisposes to malignancy....

"Although cardia-type epithelium might be a risk factor for malignancy, the magnitude of that risk remains unclear."

"Based on this lack of data, it is justified not to perform endoscopic surveillance for patients solely with cardia-type epithelium...."

Then these would be Barrett’s in the UK as of 2006

If these came from mucosae that looked like endoscopic Barrett’s
The new BSO Barrett’s guidelines

British Society of Gastroenterology guidelines on the diagnosis and management of Barrett’s oesophagus

Rebecca C Fitzgerald,1 Massimiliano di Pietro,1 Krish Ragunath,2 Yeng Any,3 Jin-Yong Kang,3 Peter Watson,5 Nigel Trudgill,6 Praful Patel,7 Philip V Kaye,8 Scott Sanders,9 Maria O’Donovan,10 Elizabeth Bird-Lieberman,11 Pradeep Bhandari,12 Janusz A Jankowski,13 Stephen Attwood,14 Simon L Parsons,15 Duncan Loft,16 Jesper Lagergren,17 Paul Moayyed,18 Georgios Lyrazopoulos,19 John de Caestecker20

Gut, 2014;63:7-42

British Society of Gastroenterology guidelines 2014

BO: any portion of the normal distal squamous epithelial lining that has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (≥1 cm) .... and is confirmed microscopically from biopsies.....

Old: Has both endo and histo requirements
New: A minimum length is now defined.


....The BSG suggests that IM not be required for the definition of BO, but it (the lack of IM) should be taken into account when deciding on the clinical management......
.....even though the insistence of the identification of IM to define or confirm a diagnosis of Barrett's oesophagus is problematic, it is recognised that the inclusion of gastric-type mucosa in short tongues of columnar-lined oesophagus is of less clinical importance in terms of the likelihood of malignant transformation and has the potential to greatly influence the frequency of diagnosis of Barrett's oesophagus at index endoscopy and the number of patients entering into follow-up and surveillance programmes.

Long discussion by the BSG summarized in the next slide


Decreasing the requirement for goblet cells would increase the diagnosis of BE by 147%.

Among patients with short columnar segments, 12% had goblet cells on subsequent endoscopy, so most of the columnar mucosa might represent proximal stomach.

No patient without goblet cells developed carcinoma.

Decreasing the requirement for goblet cells would cause many patients to be inaccurately labeled as BE.

.....non-IM columnar mucosa has little cancer risk, and inclusion of it in the BO diagnosis will greatly increase the number of people on surveillance who don’t need it.


Decreasing the requirement for goblet cells would increase the diagnosis of BE by 147%.

Among patients with short columnar segments, 12% had goblet cells on subsequent endoscopy, so most of the columnar mucosa might represent proximal stomach.

No patient without goblet cells developed carcinoma.

Decreasing the requirement for goblet cells would cause many patients to be inaccurately labeled as BE.

Sounds like a waste of time, resouces and money to include these people!
What happens to people with non-IM columnar lined lower esophagus (CLE) over time? There is limited long-term follow-up data.

U of Chicago study: 12% of CLE patients without IM developed goblet cells on F-U exam within 5.8 years. 

Houston VA study: 29% of CLE patients without IM developed goblet cells on F-U exam within 2 years

Does non-IM CLE have a cancer risk? There is very little data.

U of Chicago study, 2012:
No patient without IM developed carcinoma, over a mean F-U of 5.8 years. This is a small series, and 5.8 years is not long enough.

Northern Ireland study, 2011
8,522 Barrett's pts, mean 7 years FU
Incidence/yr of esoph/cardia AdCA

<table>
<thead>
<tr>
<th></th>
<th>With IM</th>
<th>Without IM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.38%</td>
<td>0.07%</td>
</tr>
</tbody>
</table>

I have not mentioned surveillance and diagnosing dysplasias. That requires a 2 hour lecture accompanied by teeth nashing and screaming!

Are we fussing too much about goblet cells and cancer in and around the GE Junction?

Summary
Cardiac mucosa has lots of stuff that seems to be clinically unimportant. Barrett’s mucosa is so common and its cancers are so rare that most screening may be pointless. If these facts become widely accepted, the 10% of my income that comes from the GEJ will be cut substantially.

Goblet cells in the esophagus are required for the diagnosis of Barrett’s mucosa. Barrett’s mucosa is common. The diagnosis of Barrett’s mucosa leads to unpleasant surveillance endocopy and biopsy. Barrett’s carcinomas are uncommon.
Goblet cells in the cardia are common. Their link to carcinoma is pretty puny. Surveillance for cardiac IM is not recommended.

Are we fussing too much about goblet cells and cancer in and around the GE Junction?

What role do pathologists play in all this? We still have to find the damned goblet cells regardless of whether they are important. We still have to diagnose dysplasias for which there are no great criteria.

Sometimes, you just do what you gotta do!
It takes

To be a GI pathologist