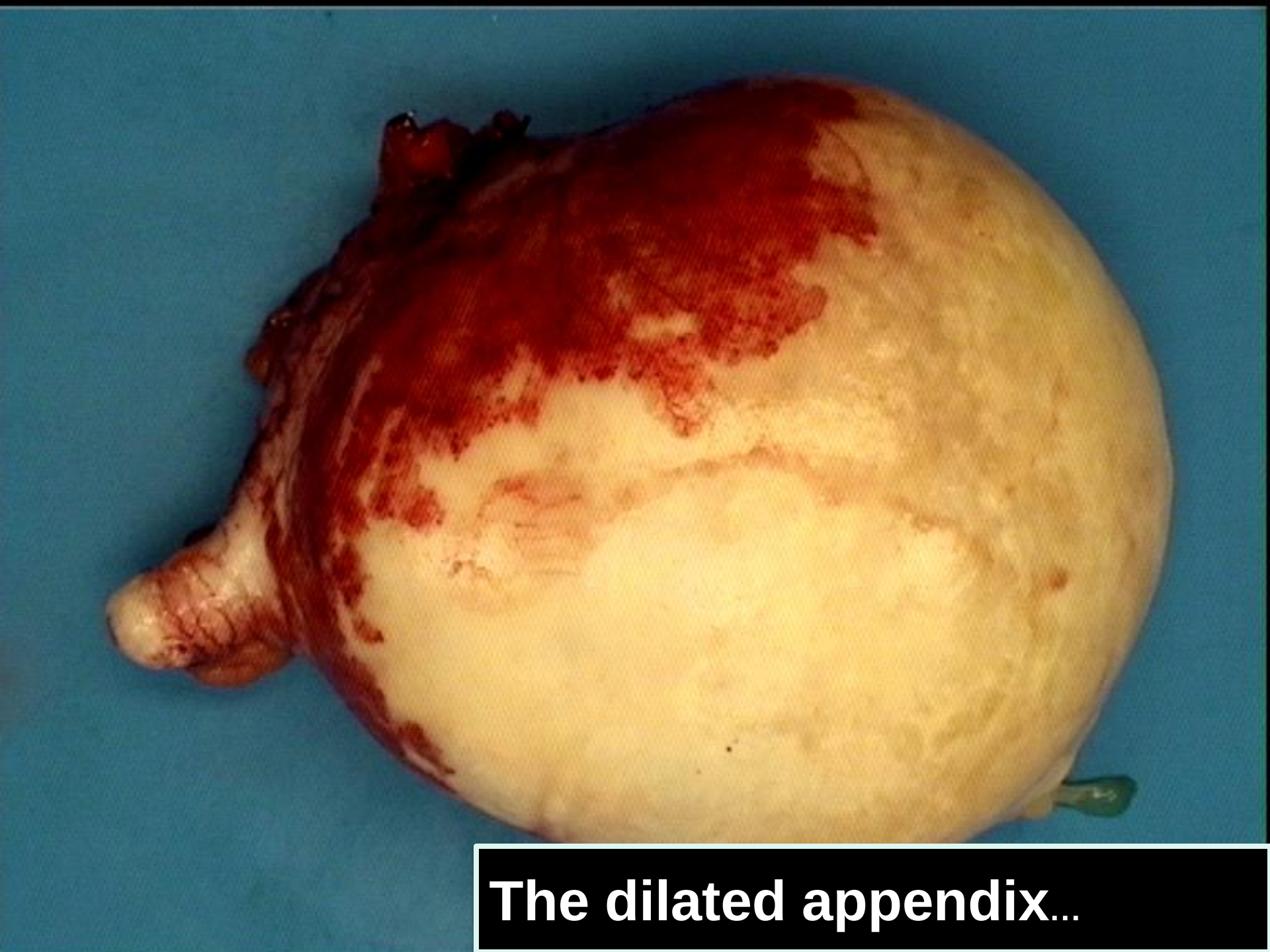
Appendiceal Mucinous Neoplasms

And Other Appendiceal Aggravations

Case History:

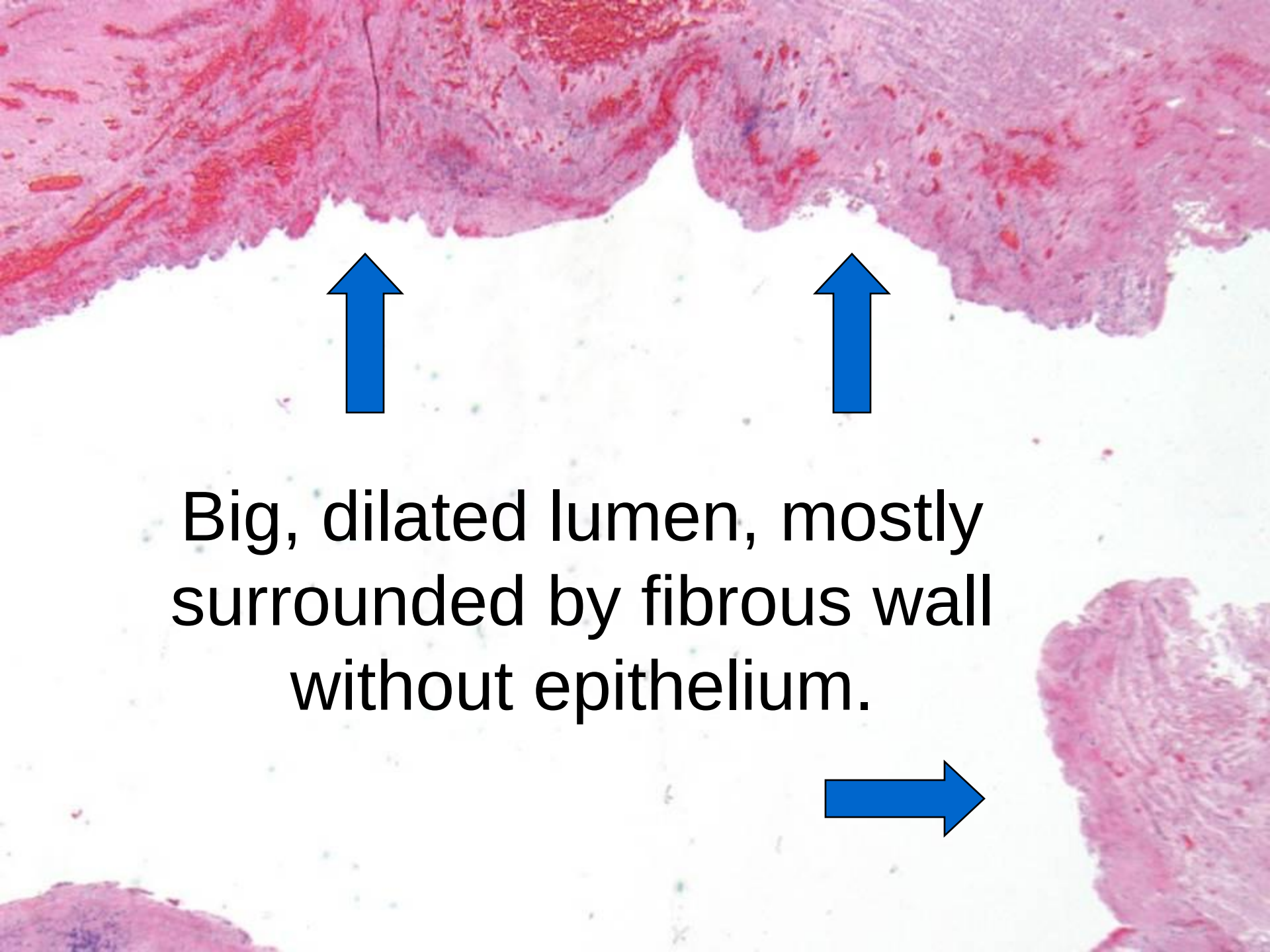
A patient presented with signs and symptoms of acute appendicitis.

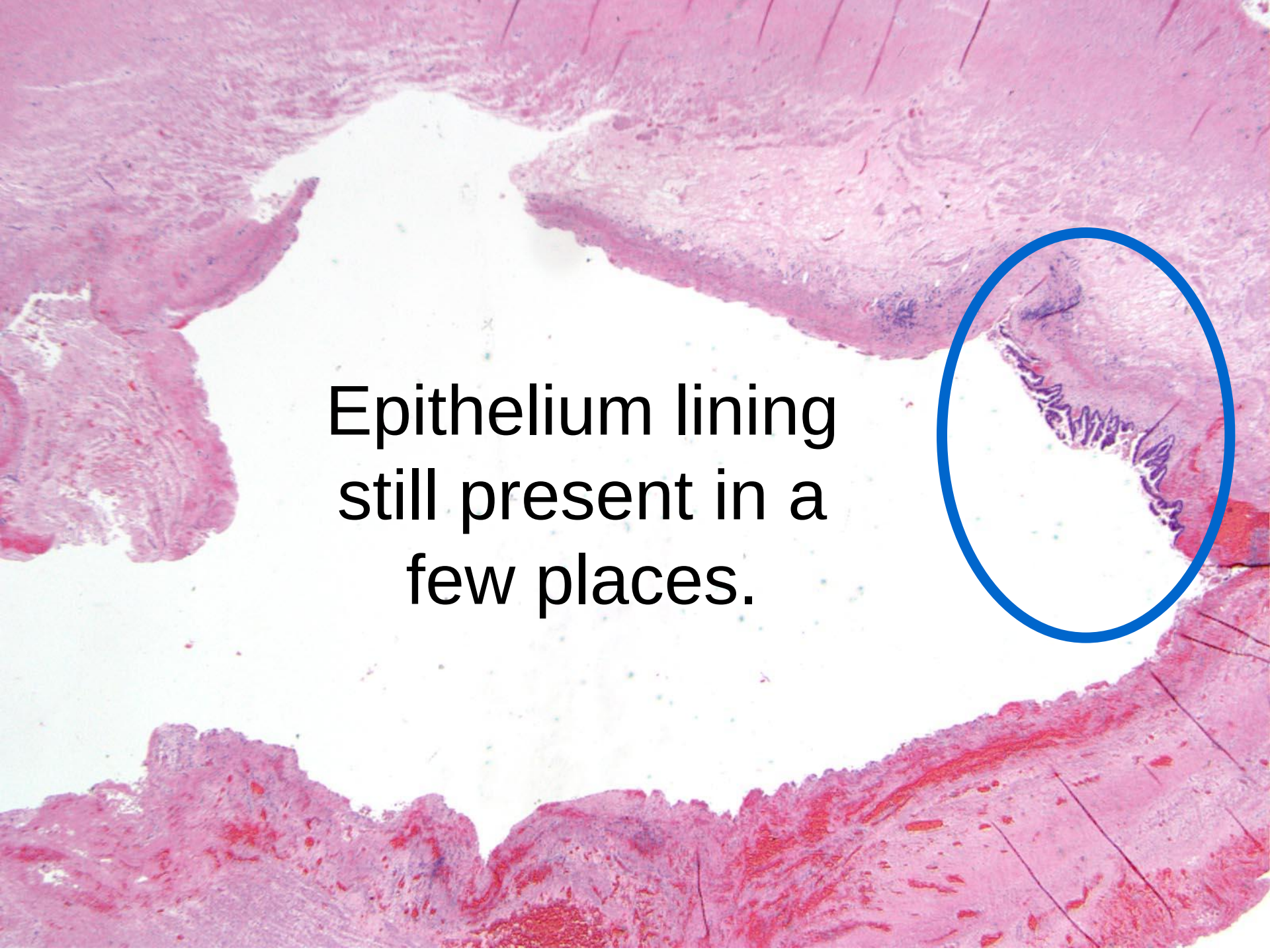
The surgeon found a large, cystically dilated appendix with mucus adherent to the tip, mucus in the pelvis surrounding the right fallopian tube and ovary, and small mucus implants on the serosa of the small bowel. She performed an appendectomy, and right salpingo-oophorectomy, and biopsied several of the peritoneal implants.

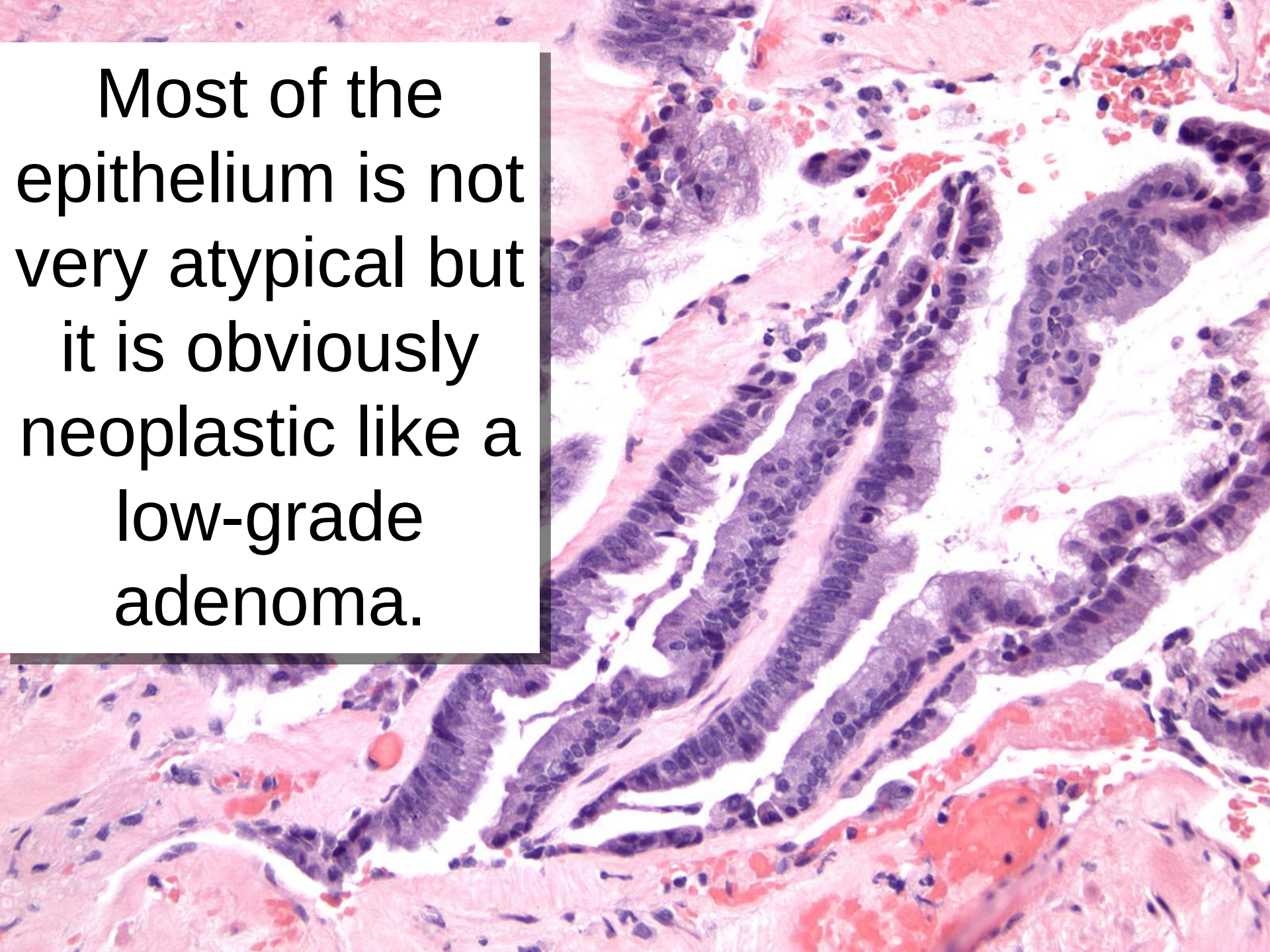

The dilated appendix...

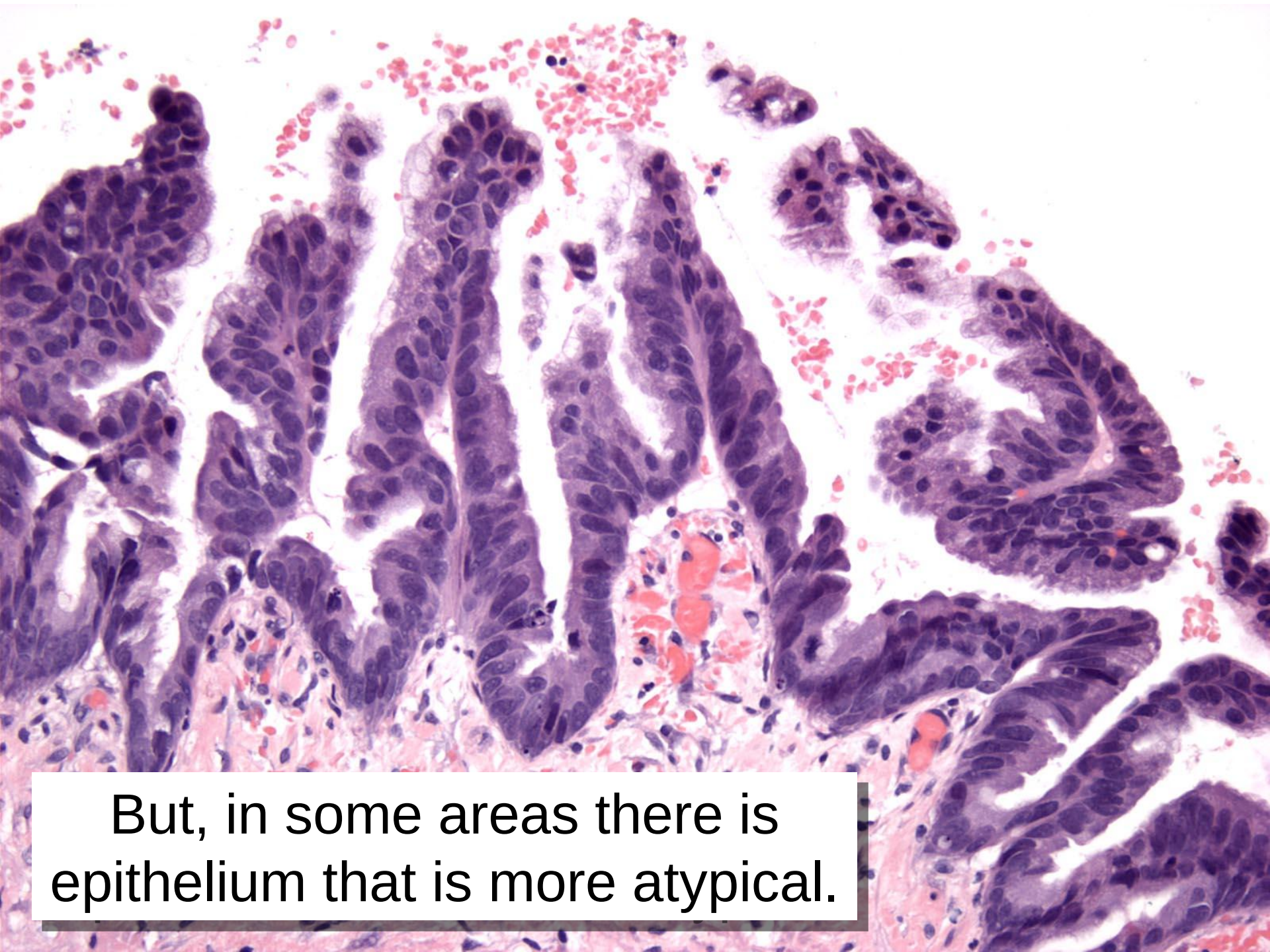
Notice that we have inked the serosal surface before sectioning

Many, many sections of appendiceal wall are examined.

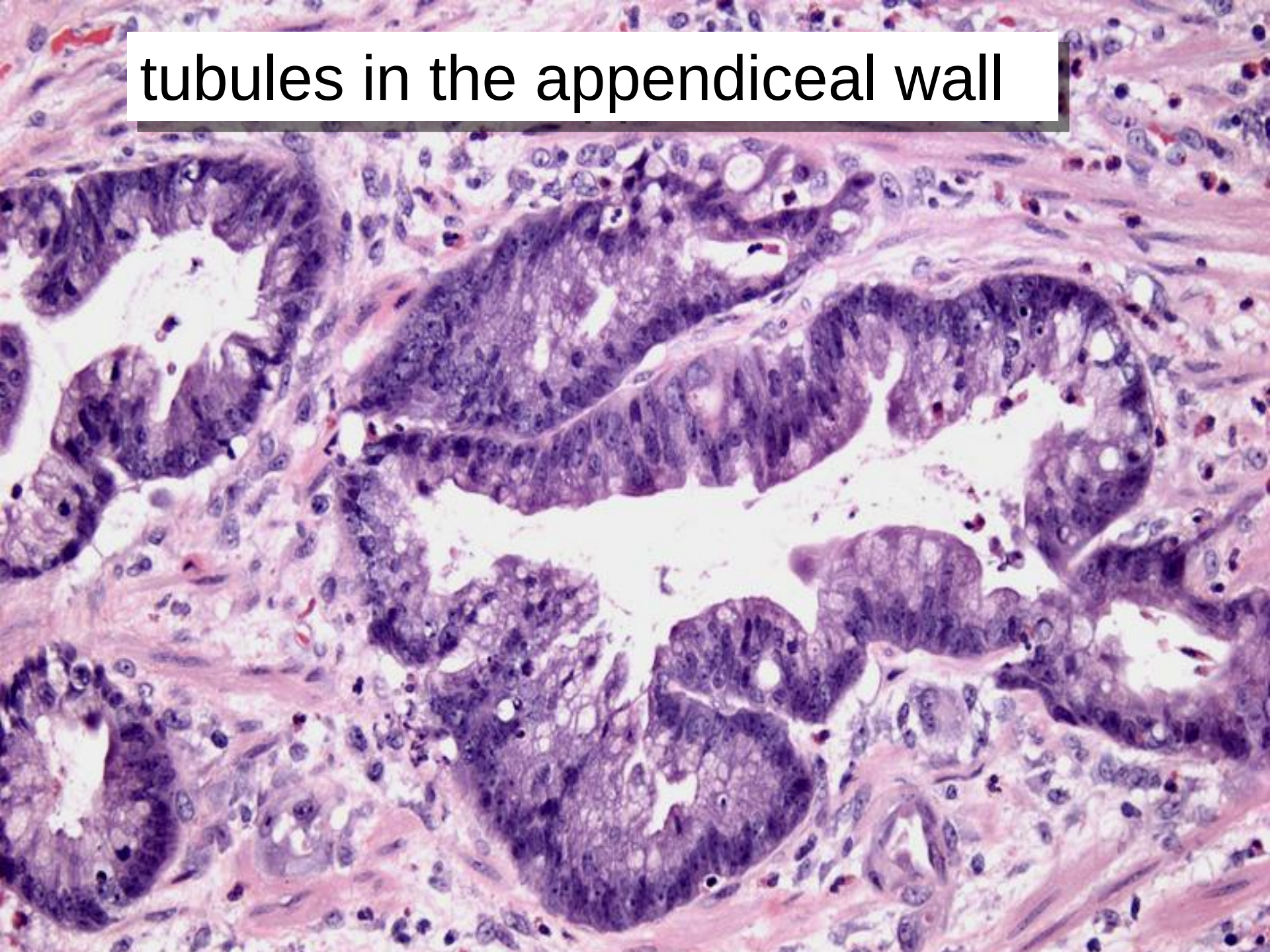

Big, dilated lumen, mostly surrounded by fibrous wall without epithelium.

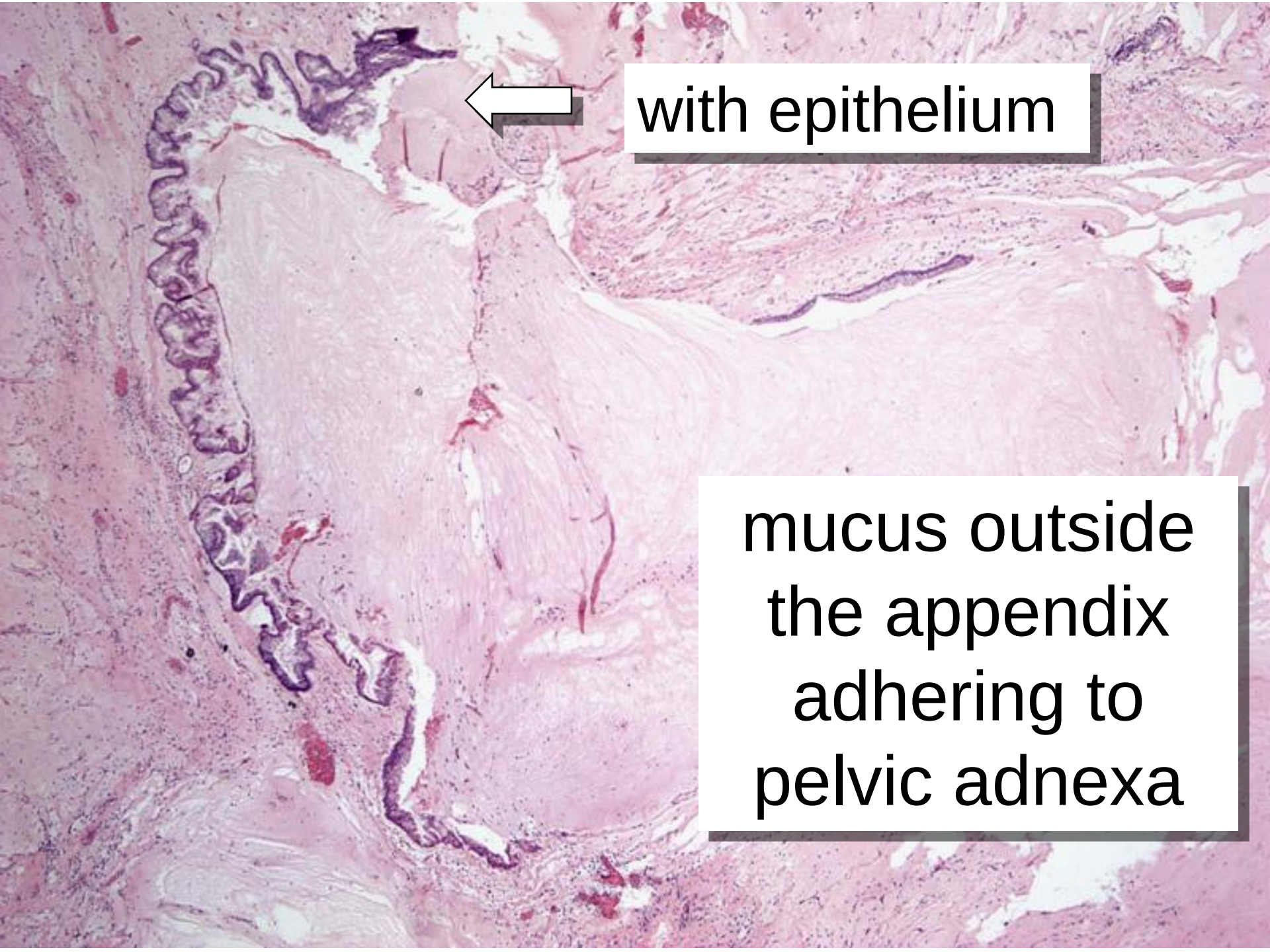

Epithelium lining still present in a few places.

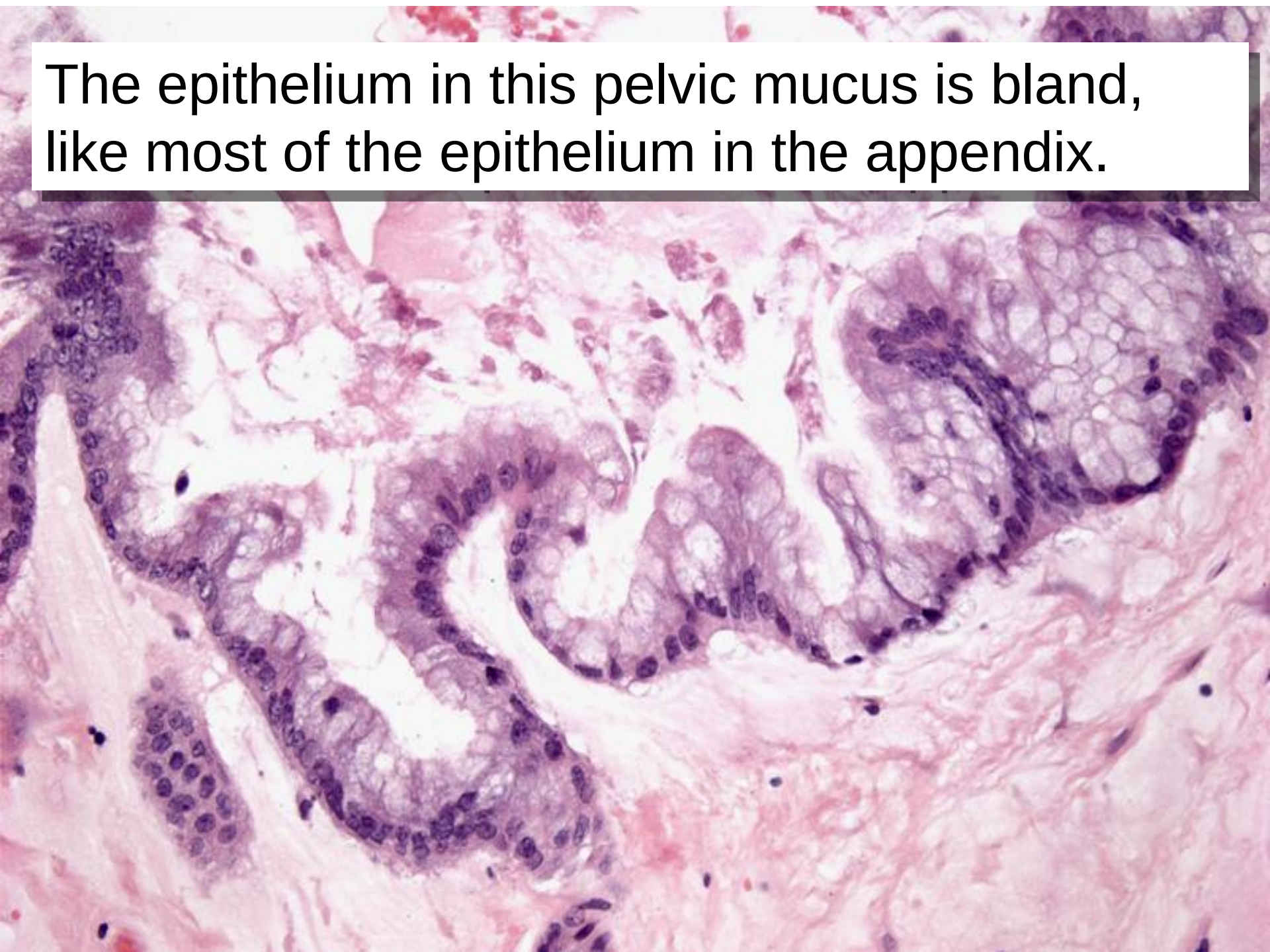

Most of the epithelium is not very atypical but it is obviously neoplastic like a low-grade adenoma.


But, in some areas there is epithelium that is more atypical.

On one slide there are irregularly shaped tubules in the appendiceal wall.


tubules in the appendiceal wall


with epithelium
mucus outside the appendix adhering to pelvic adnexa


The epithelium in this pelvic mucus is bland, like most of the epithelium in the appendix.

My first dilemma:
What is the name for this neoplasm?

Depending on the book or paper I read, I might consider a number of ways to report this case……

Appendiceal adenocarcinoma with peritoneal carcinomatosis

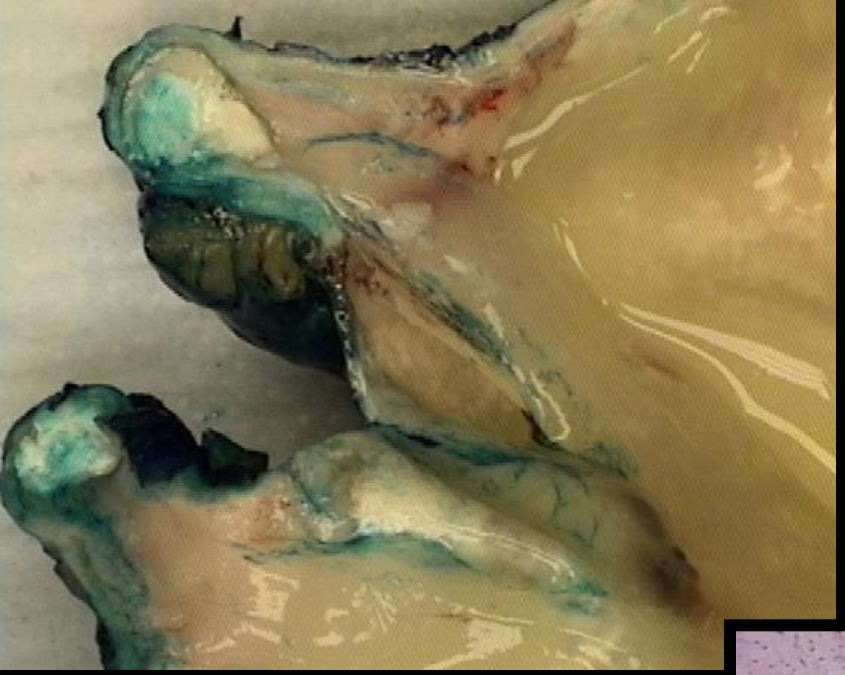
Mucinous cystadenoma of the appendix with pseudomyxoma peritonei

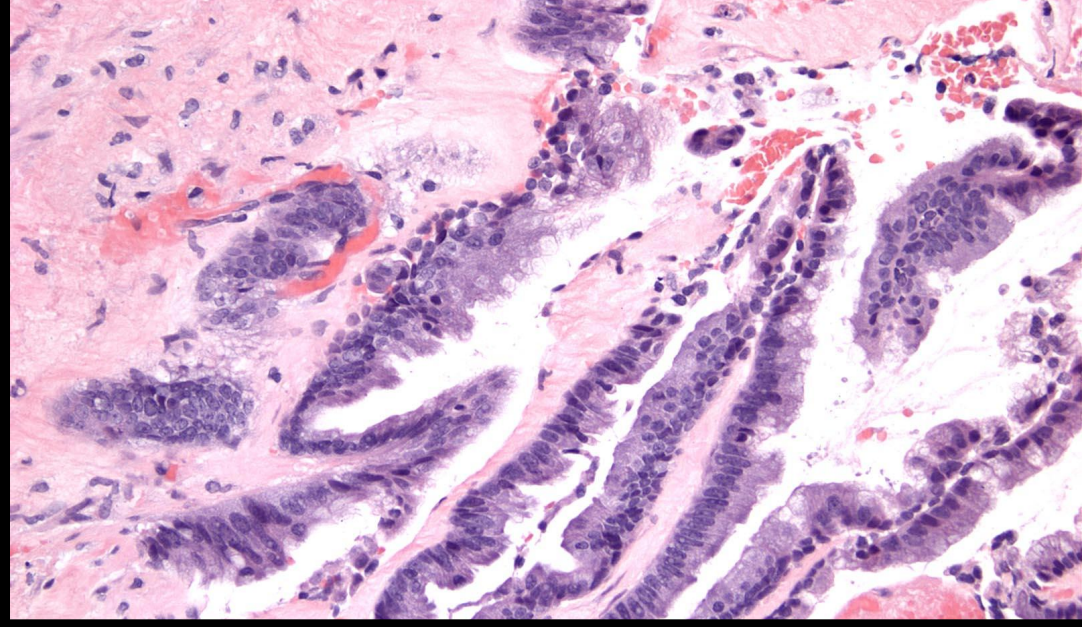
Disseminated peritoneal adenomucinosis

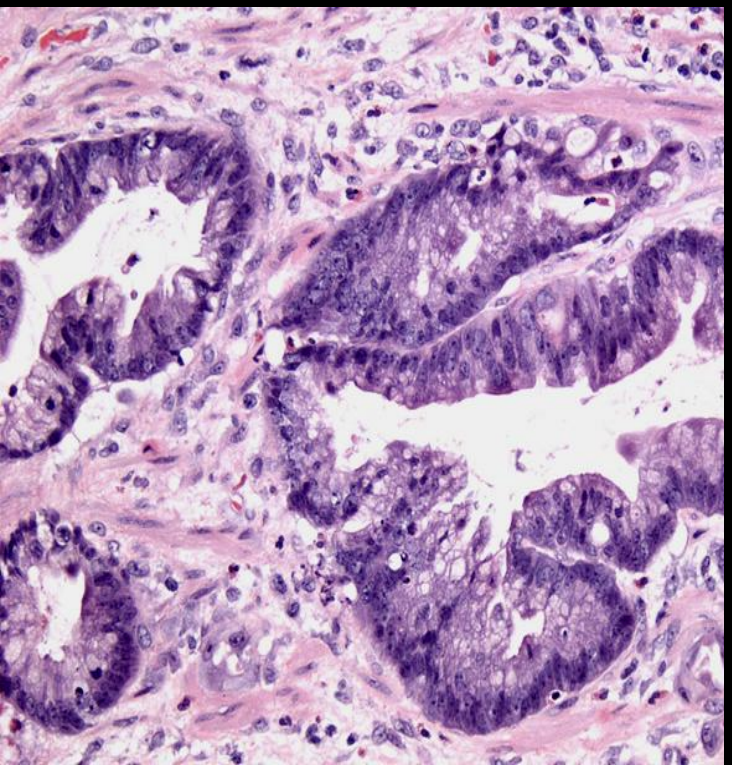
Low grade mucinous neoplasm of the appendix with peritoneal spread

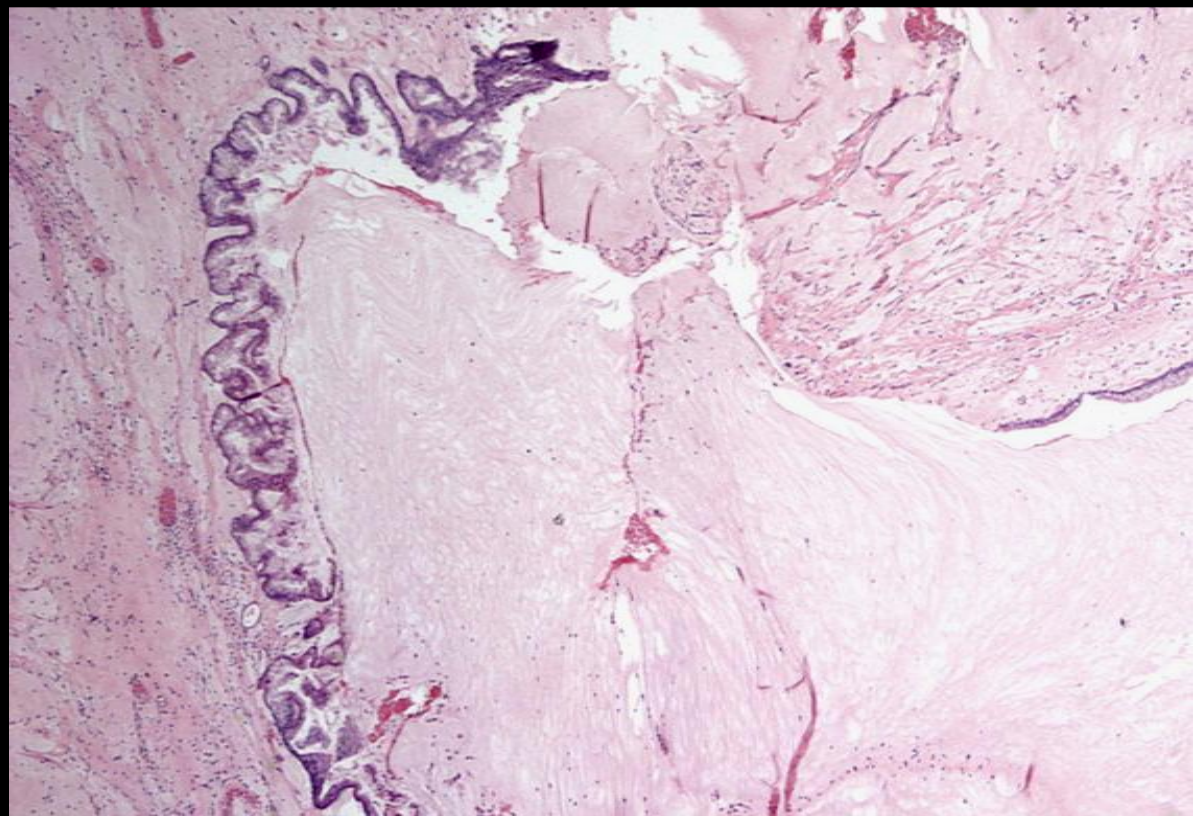
Appendiceal mucinous neoplasm of uncertain malignant potential (UMP)

What can I tell the surgeon about the prognosis?







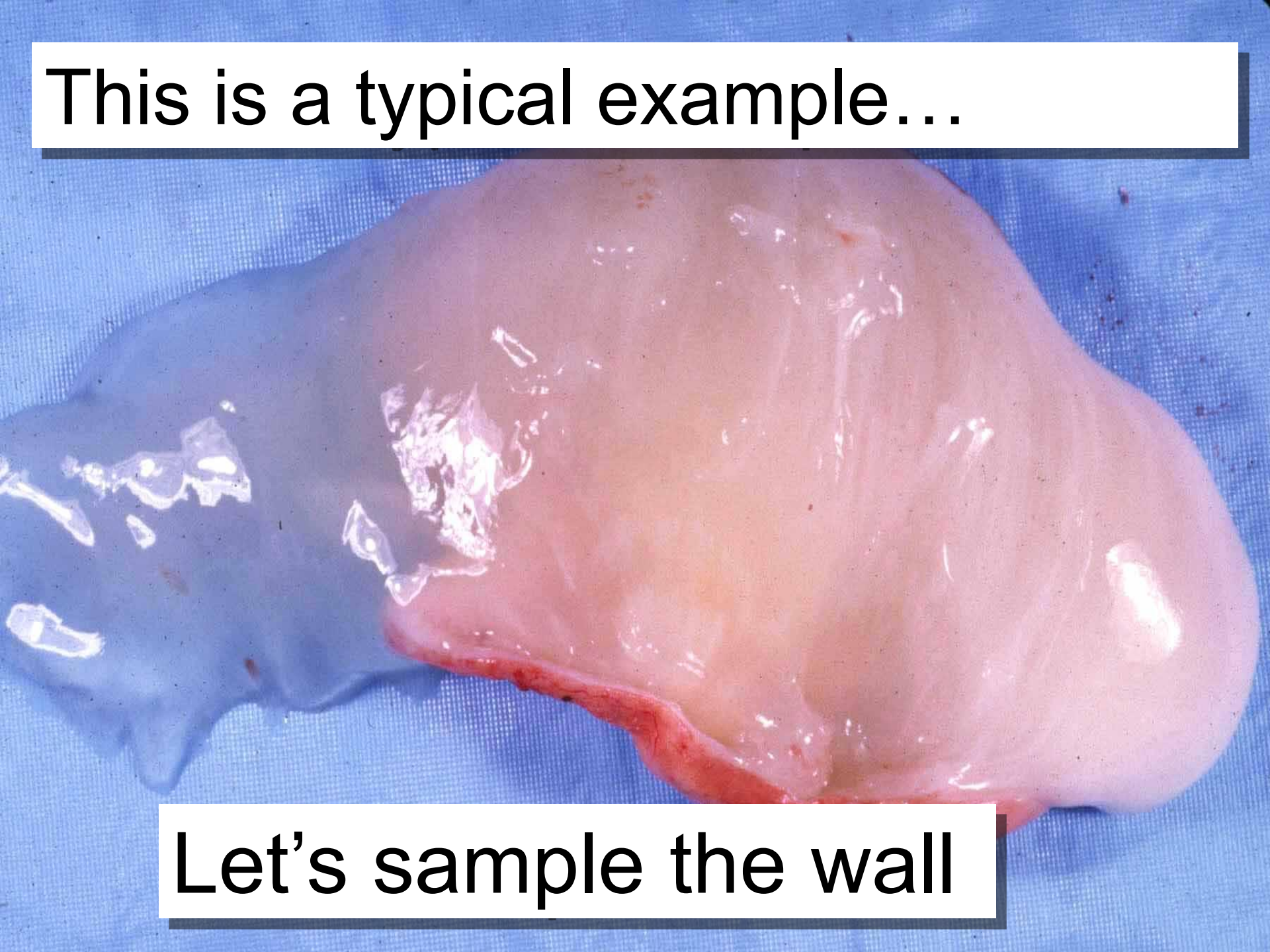


What is the correct name?

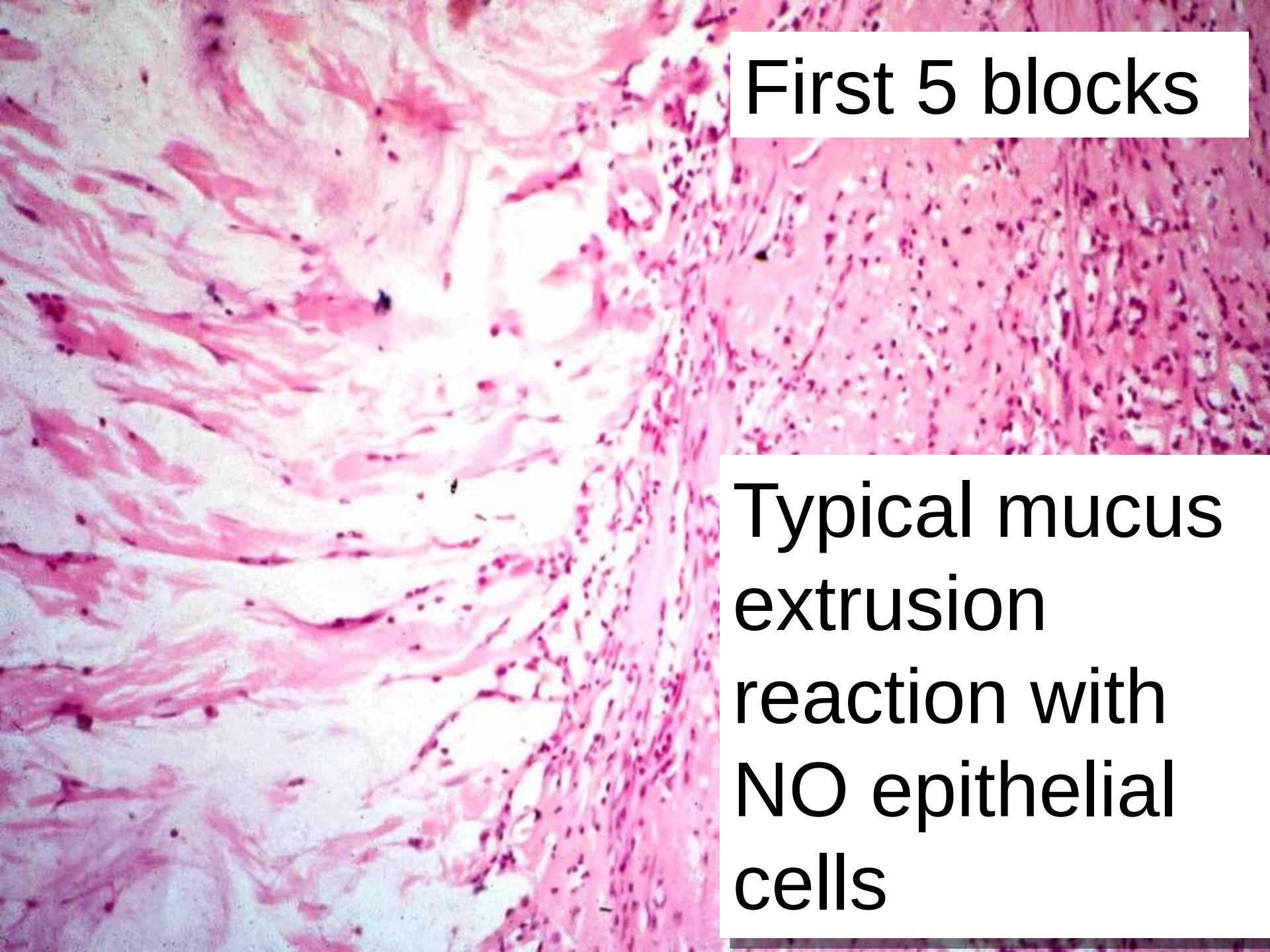
This is clearly a mucinous neoplasm of the appendix with spread to the peritoneal cavity.

What do we know about appendiceal mucinous neoplasms?

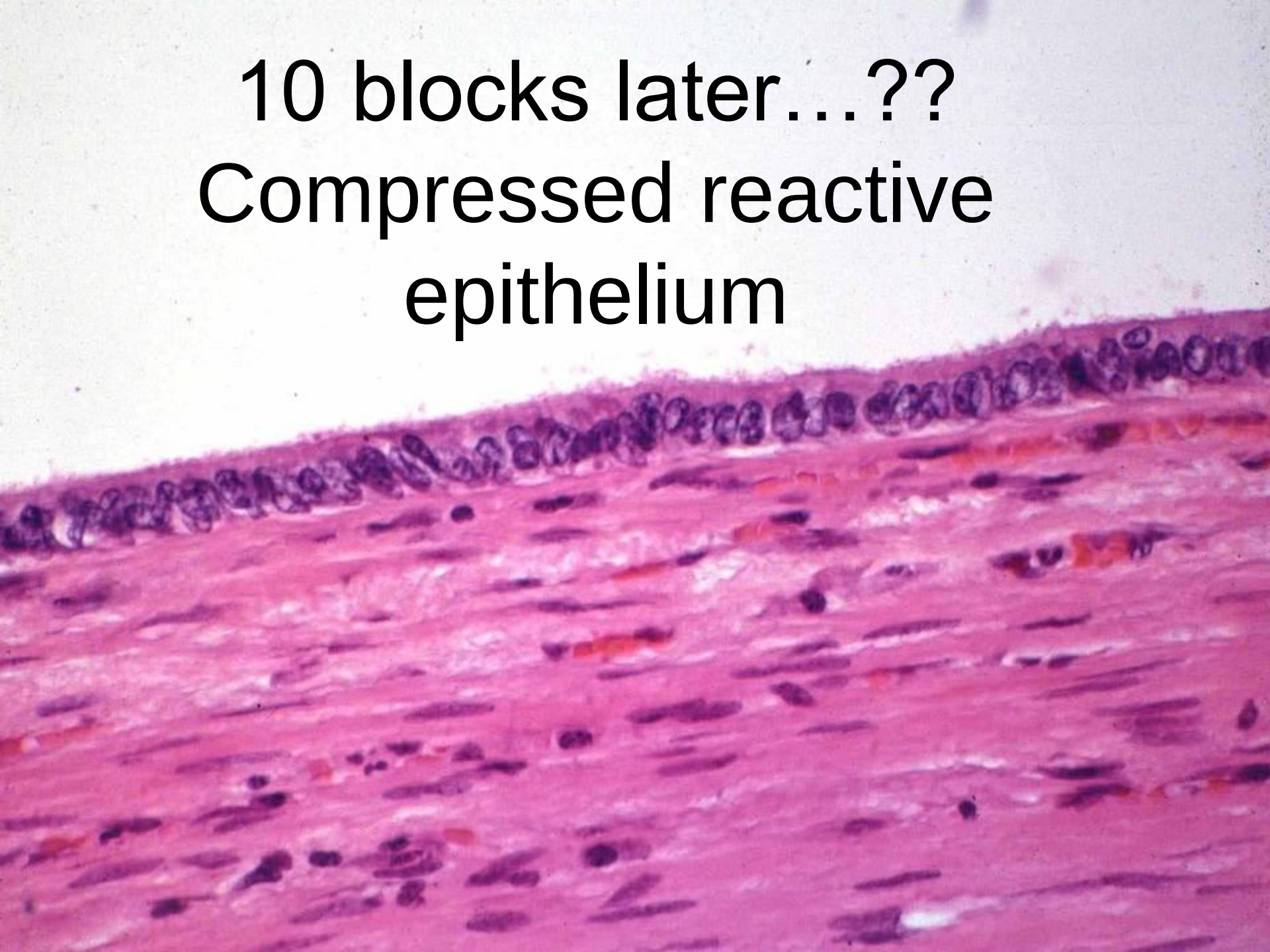
This is a typical example…



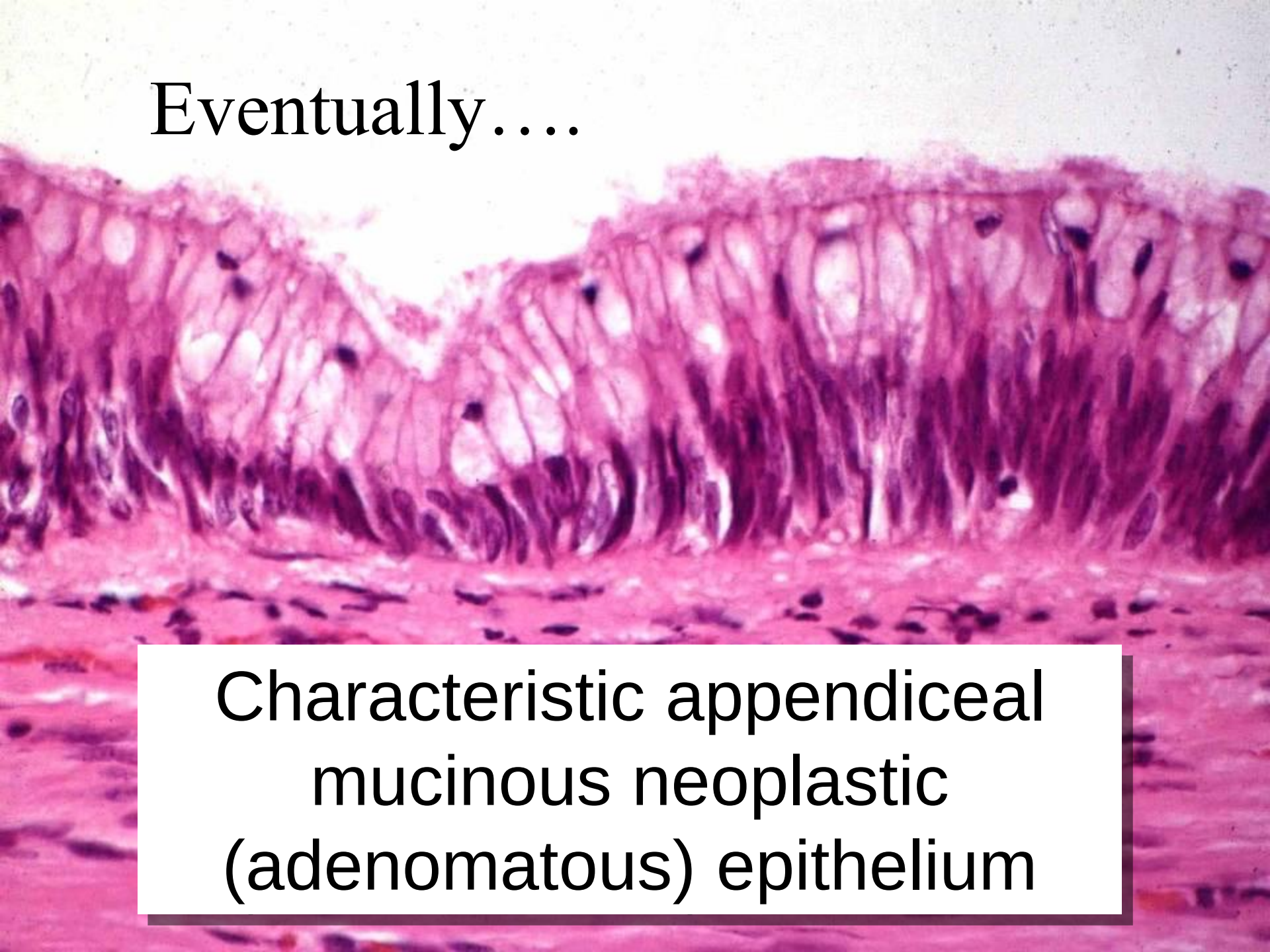
Let’s sample the wall


First 5 blocks
Typical mucus extrusion reaction with NO epithelial cells

10 blocks later…??
Compressed reactive epithelium

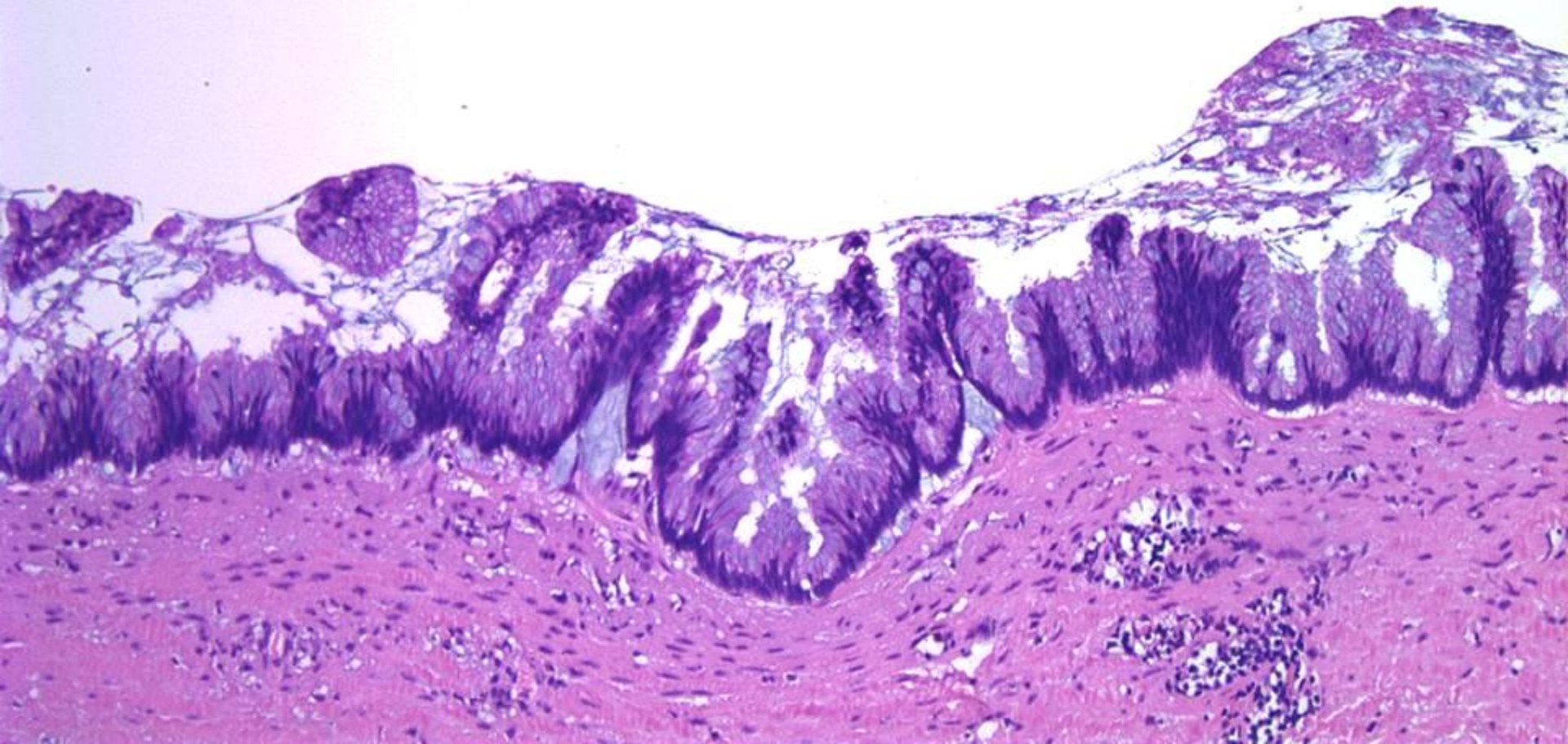


Eventually….

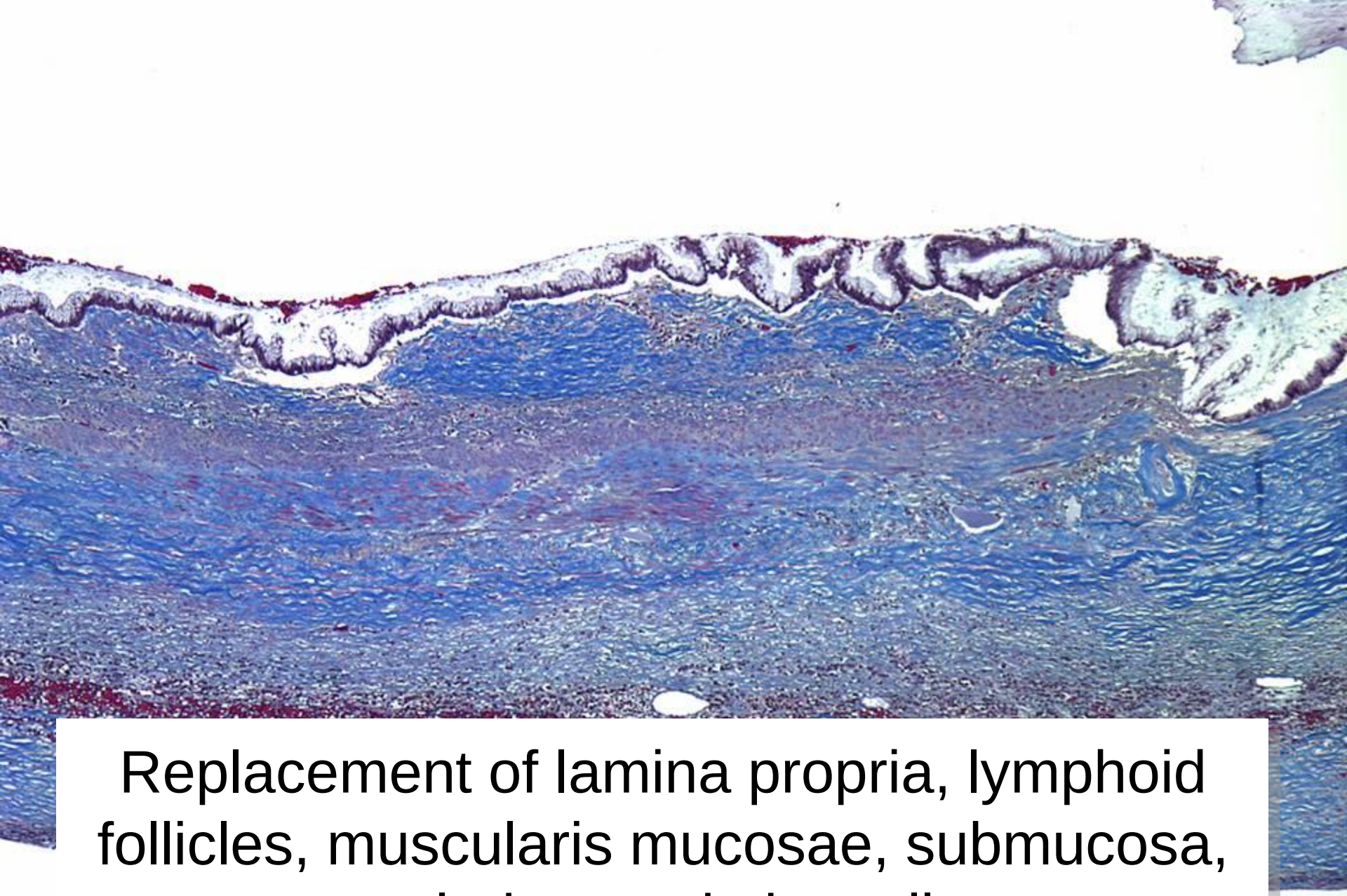


Characteristic appendiceal mucinous neoplastic (adenomatous) epithelium

Undulating, abundant cytoplasm, abundant mucin

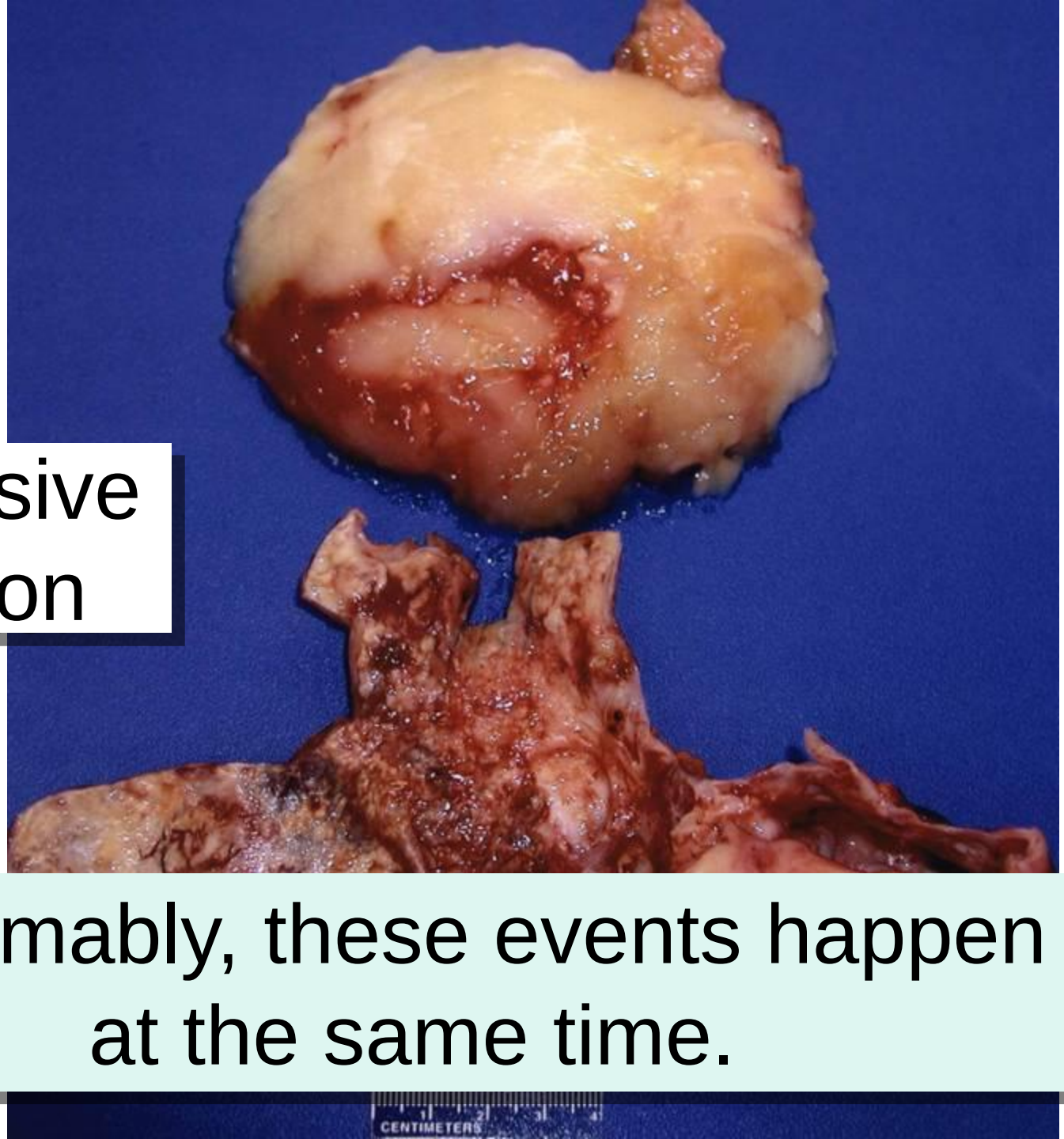



Circumferential
proliferation ± villi



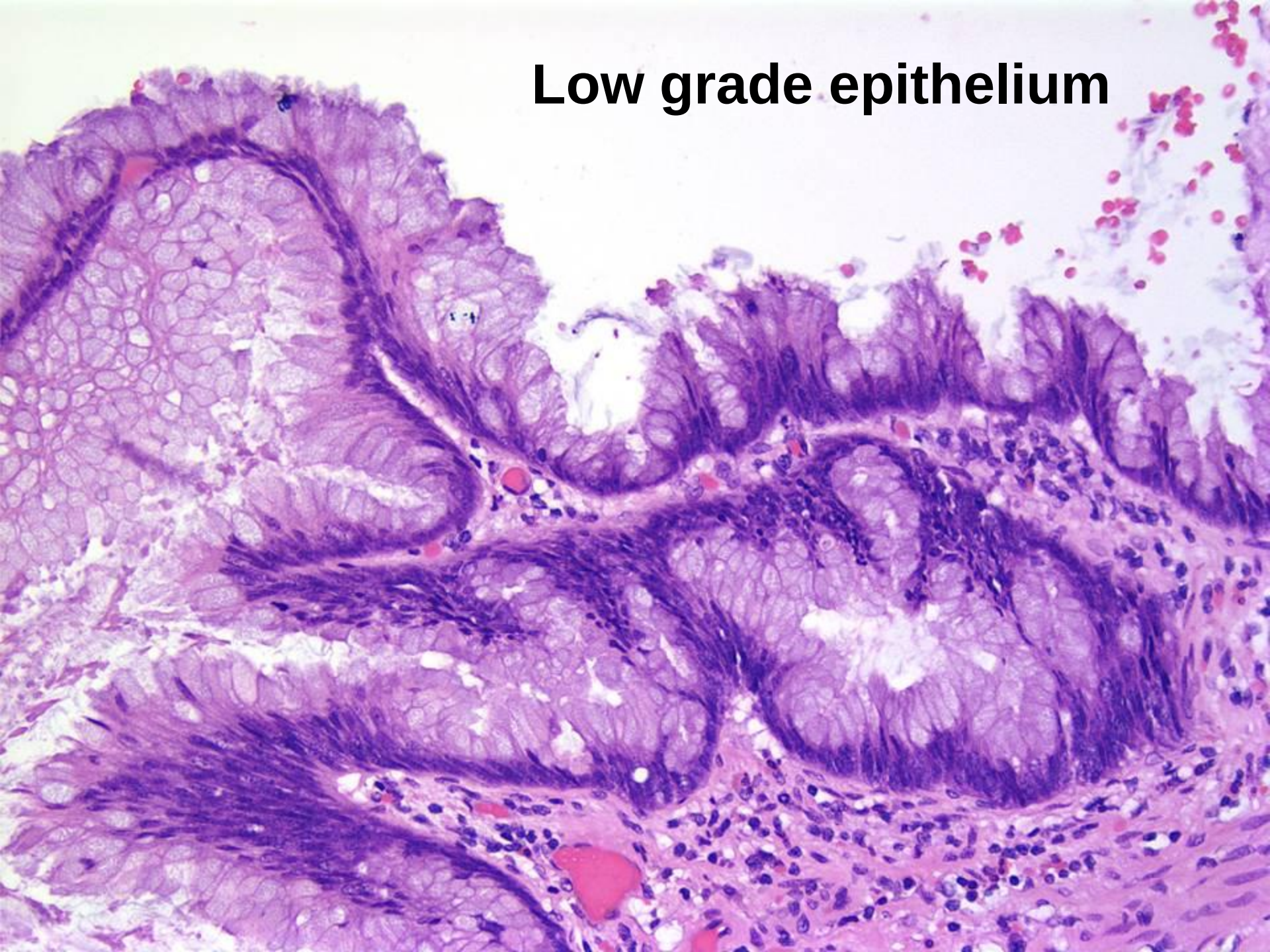
Replacement of lamina propria, lymphoid follicles, muscularis mucosae, submucosa, muscularis propria by collagen

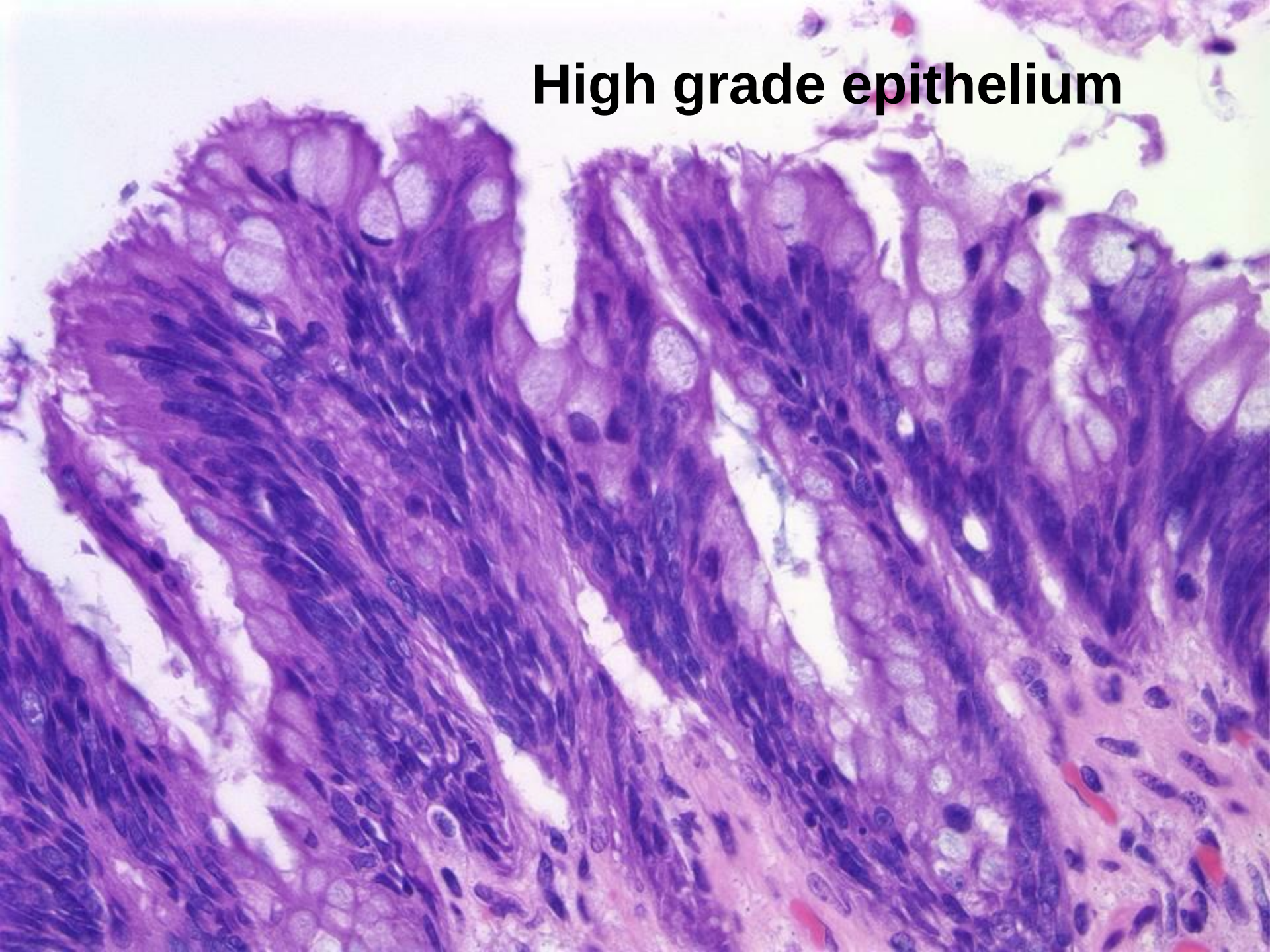
Progressive dilatation

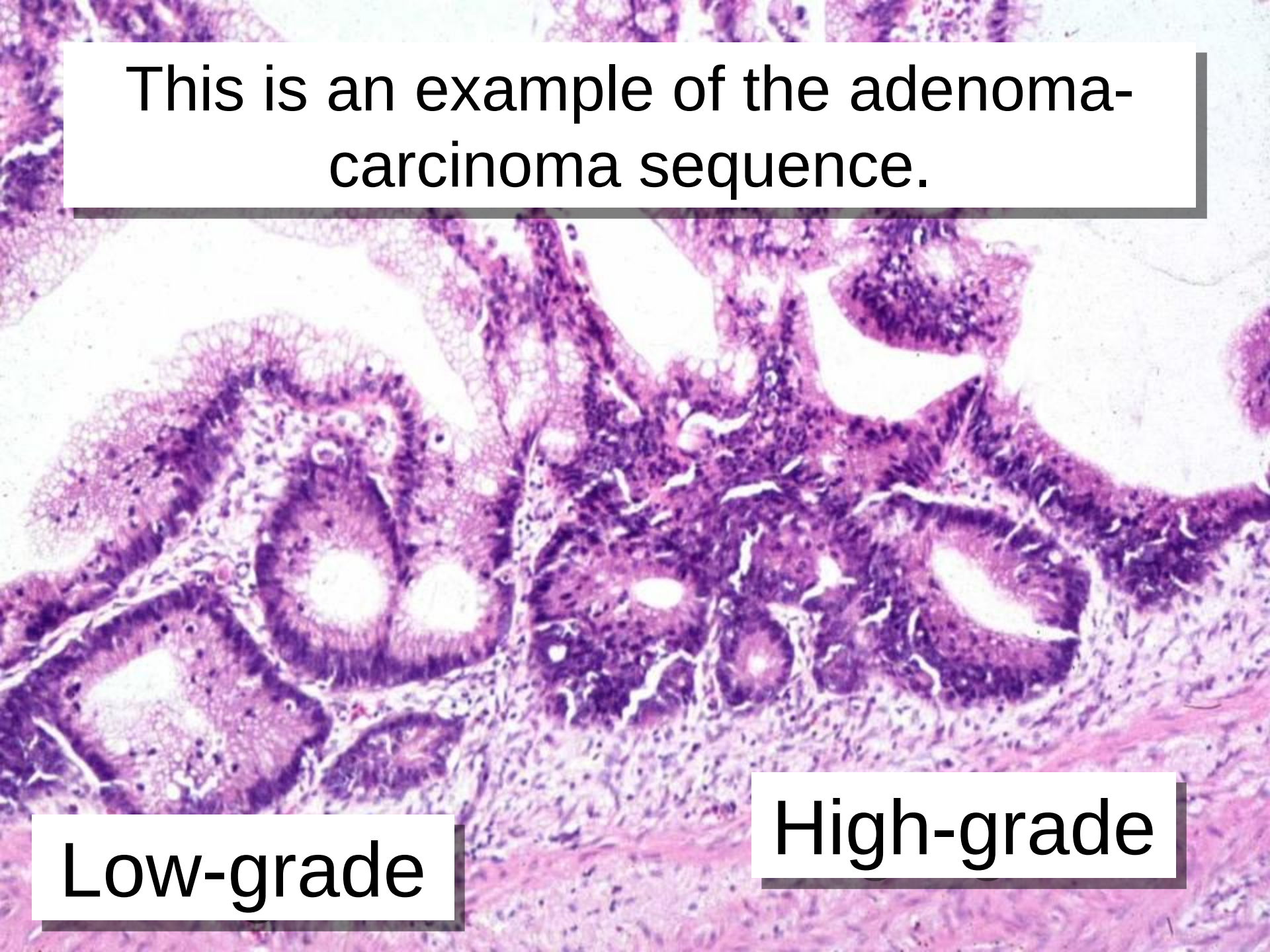


Presumably, these events happen at the same time.

Low grade epithelium

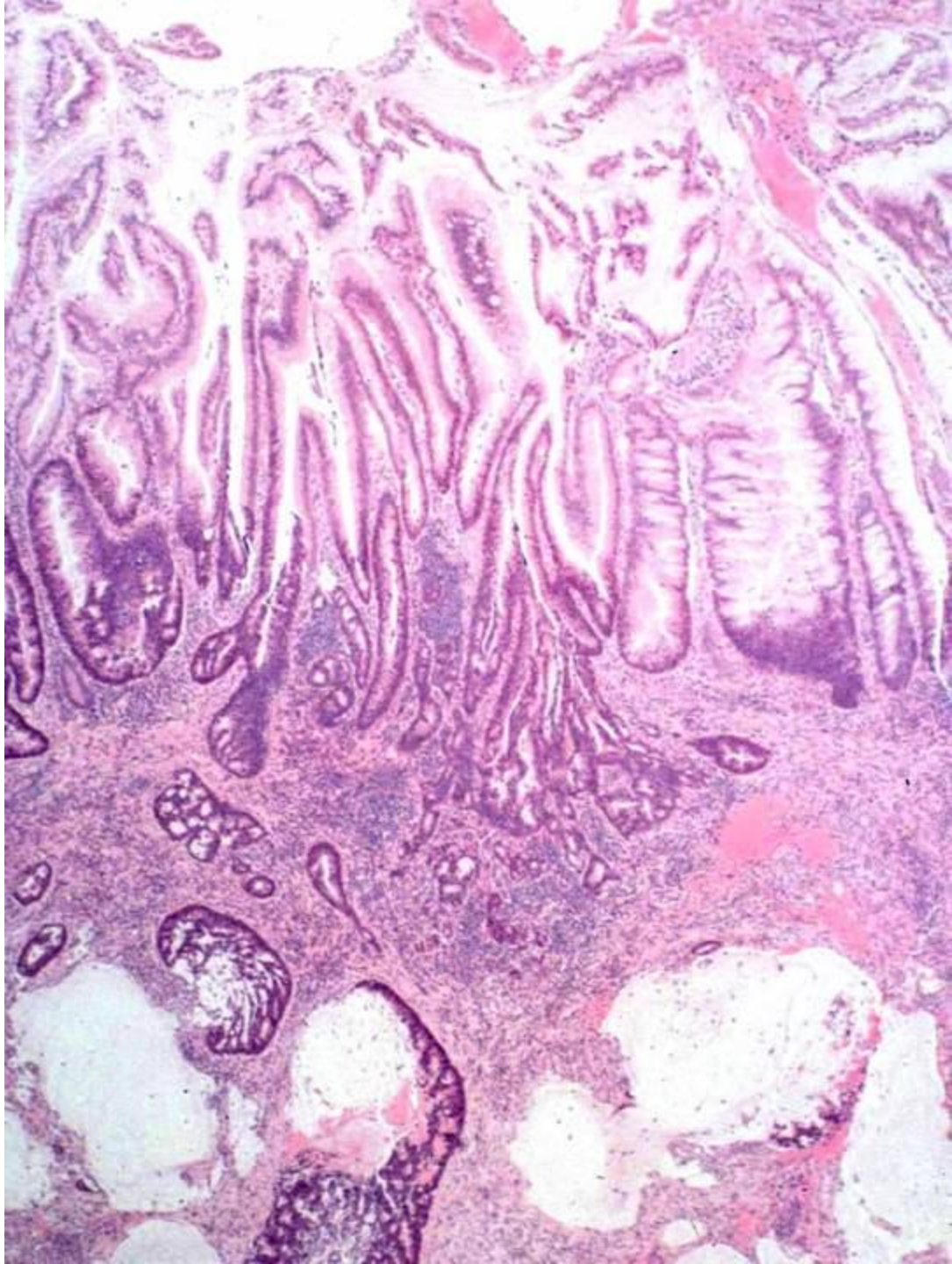



High grade epithelium

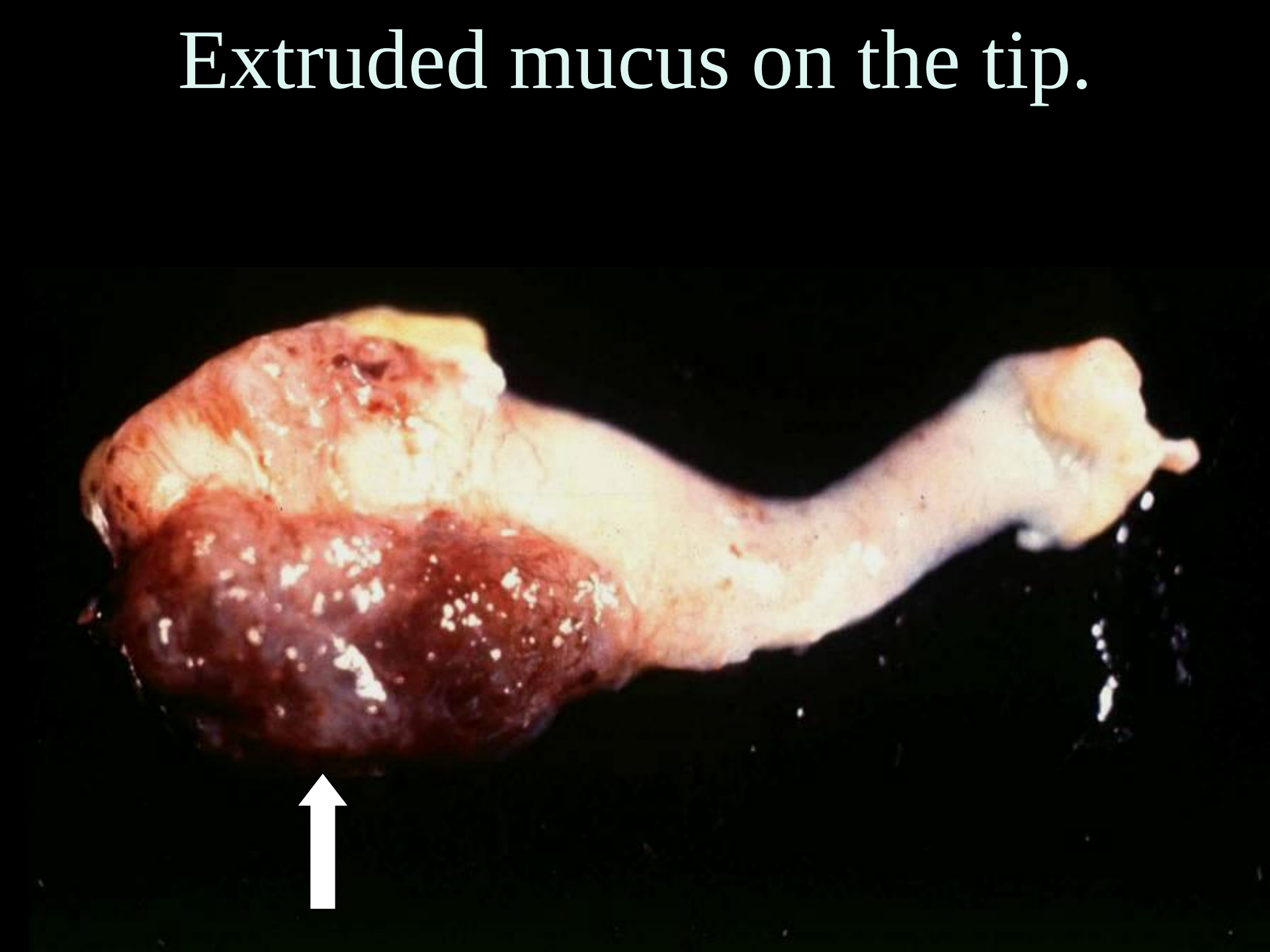

This is an example of the adenoma-carcinoma sequence.
Low-grade
High-grade

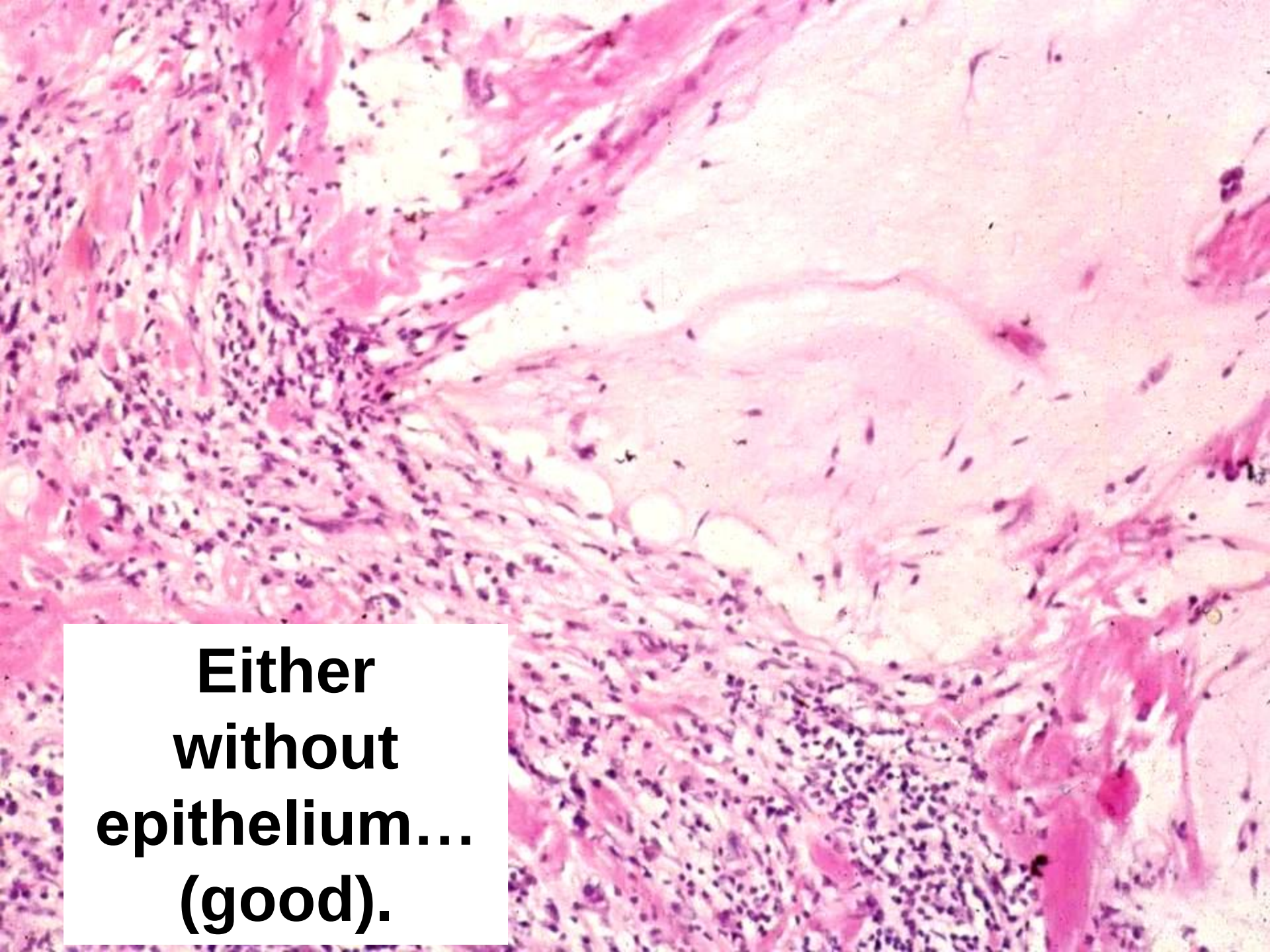
Adenoma

Carcinoma

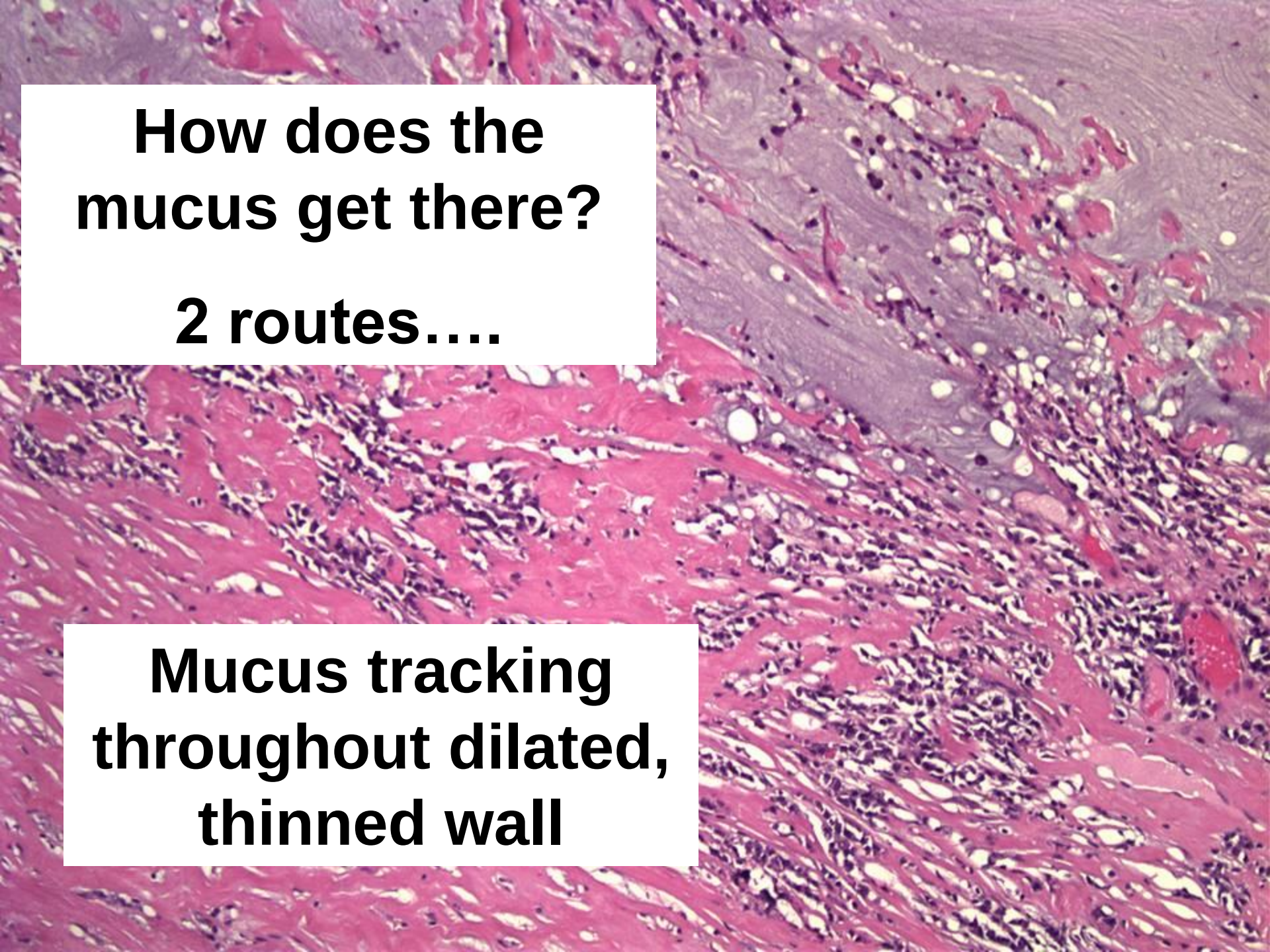


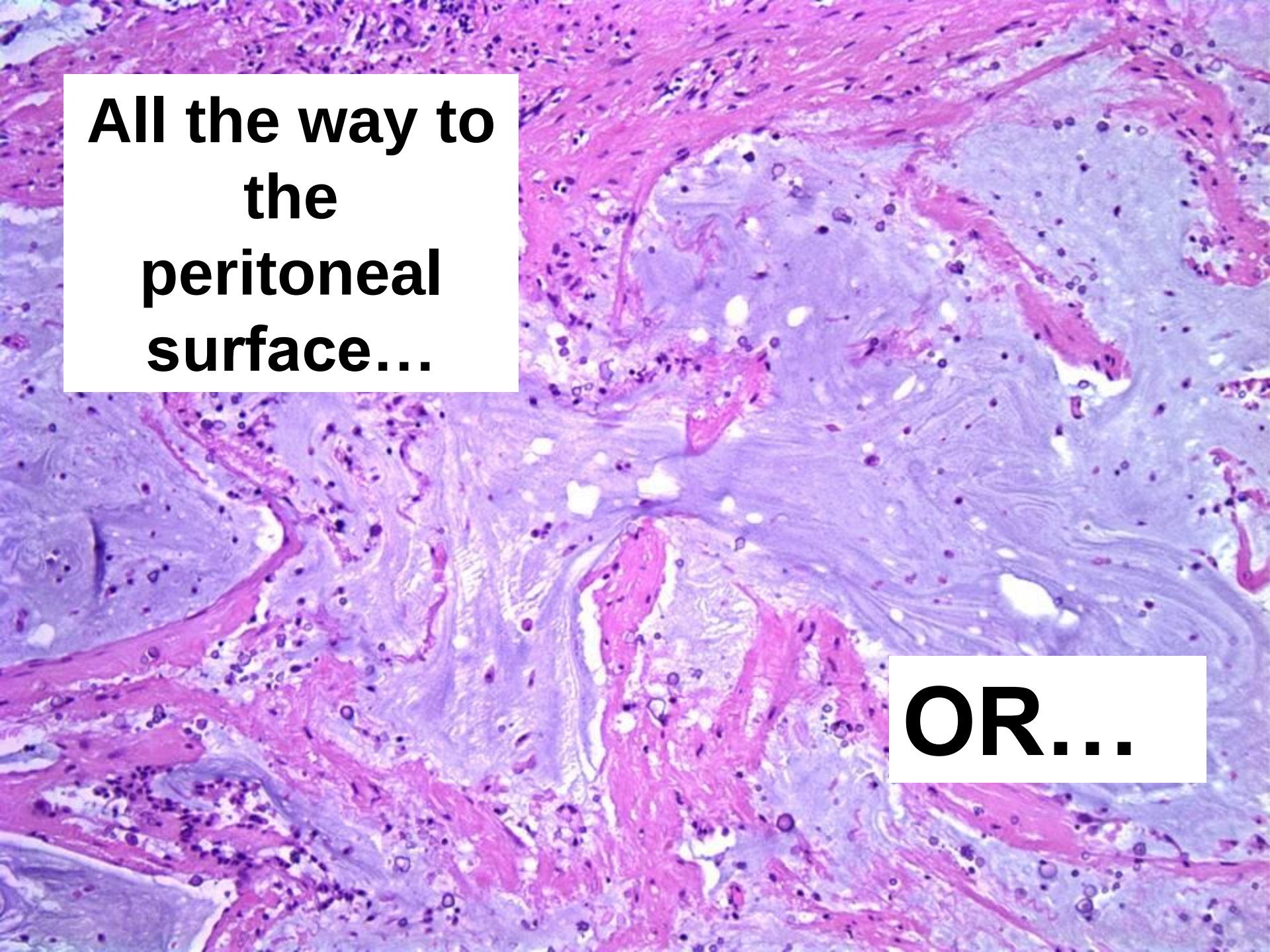
Extruded mucus on the tip.

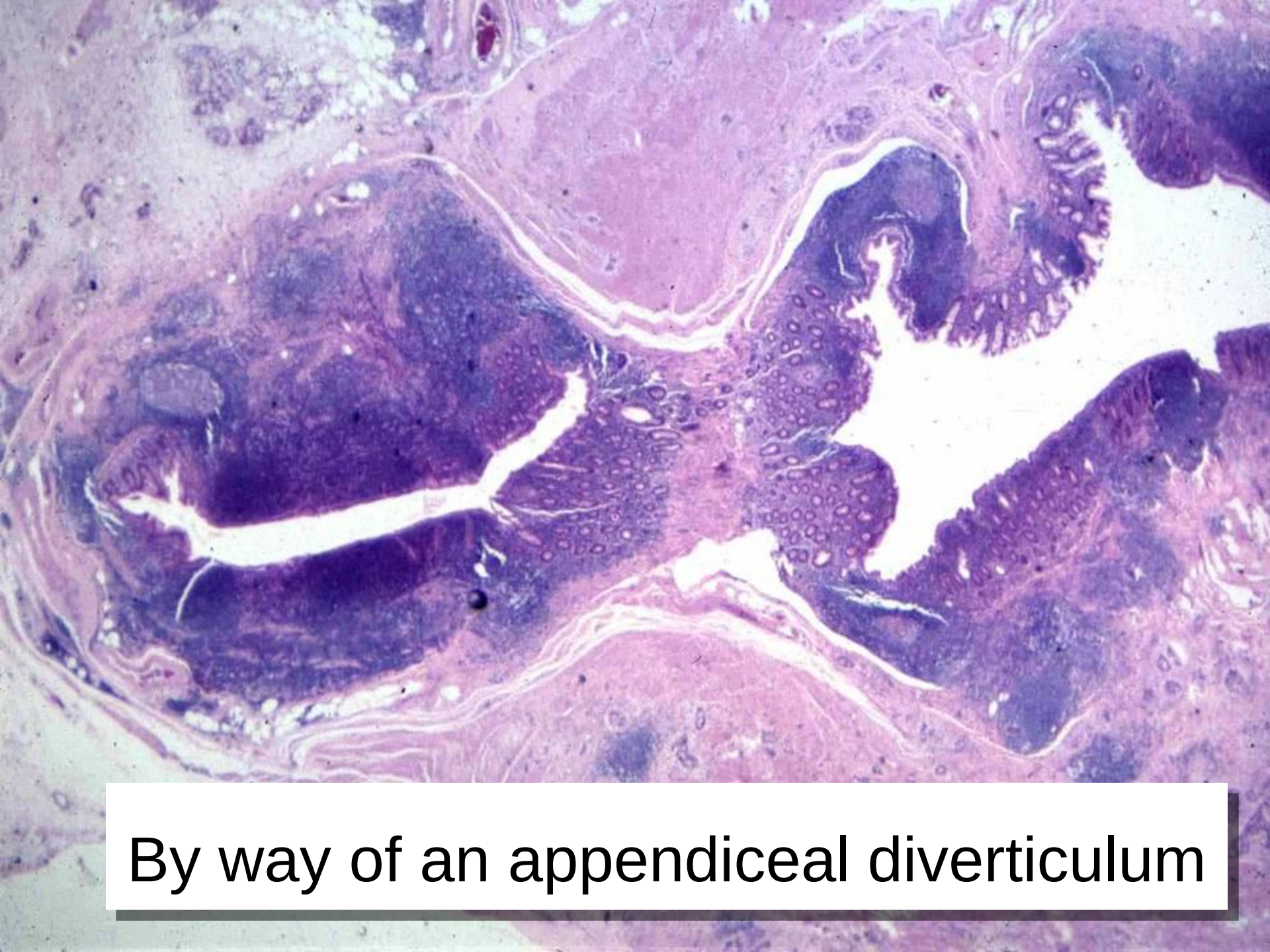



Either without epithelium… (good).

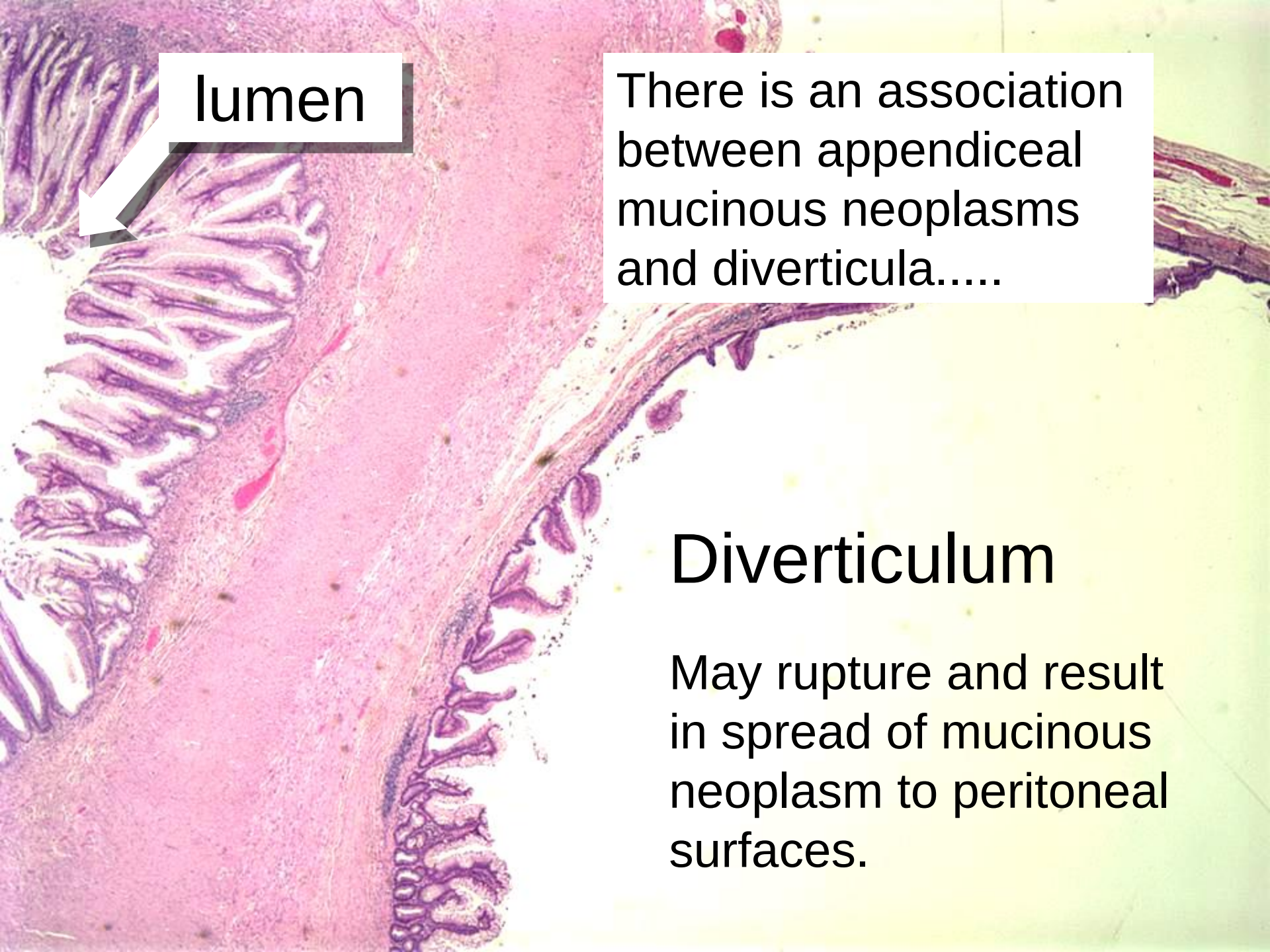

…or with epithelium
(not so good)


How does the mucus get there?
2 routes….
Mucus tracking throughout dilated, thinned wall


All the way to the peritoneal surface…
OR…



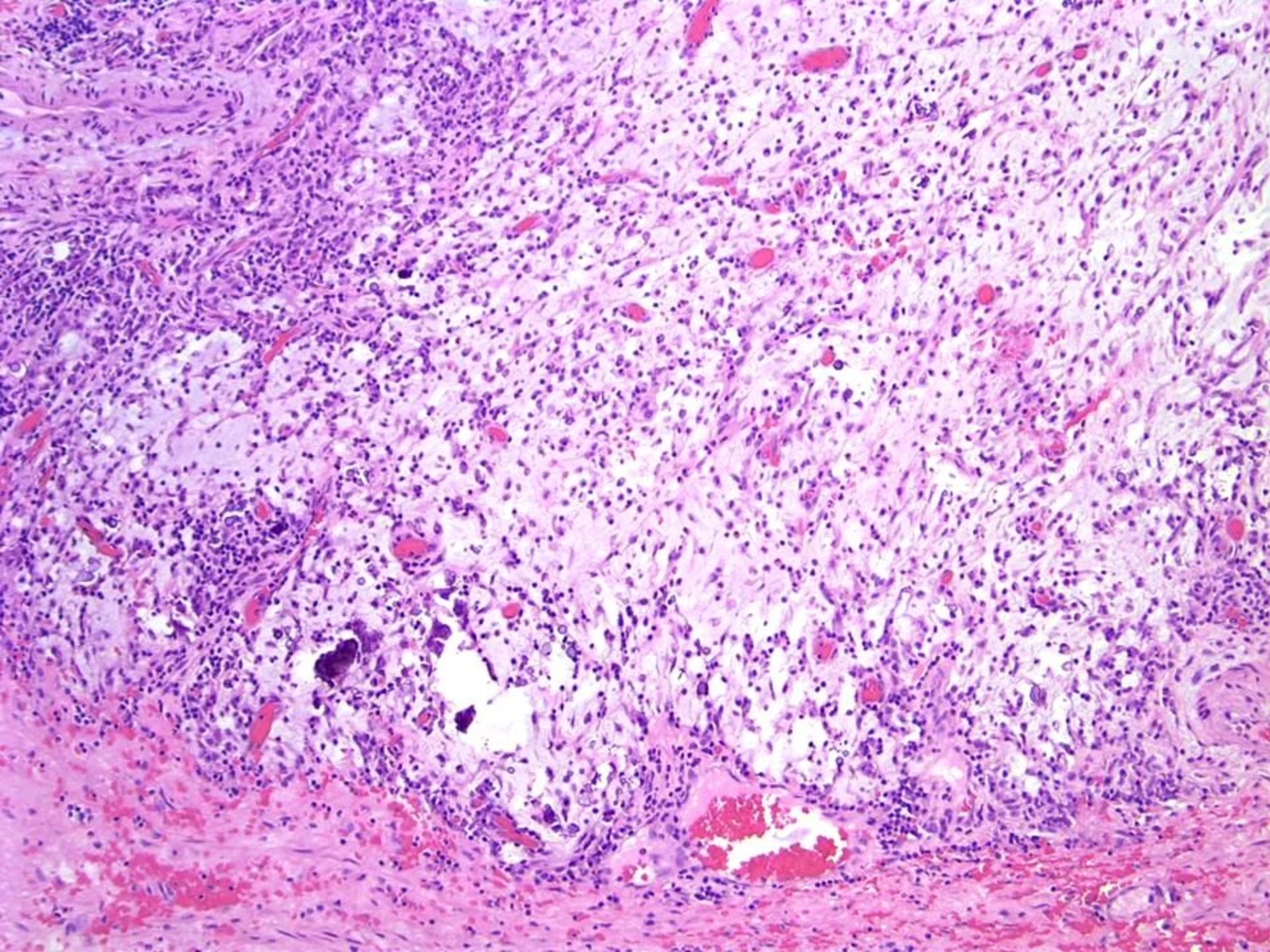
By way of an appendiceal diverticulum



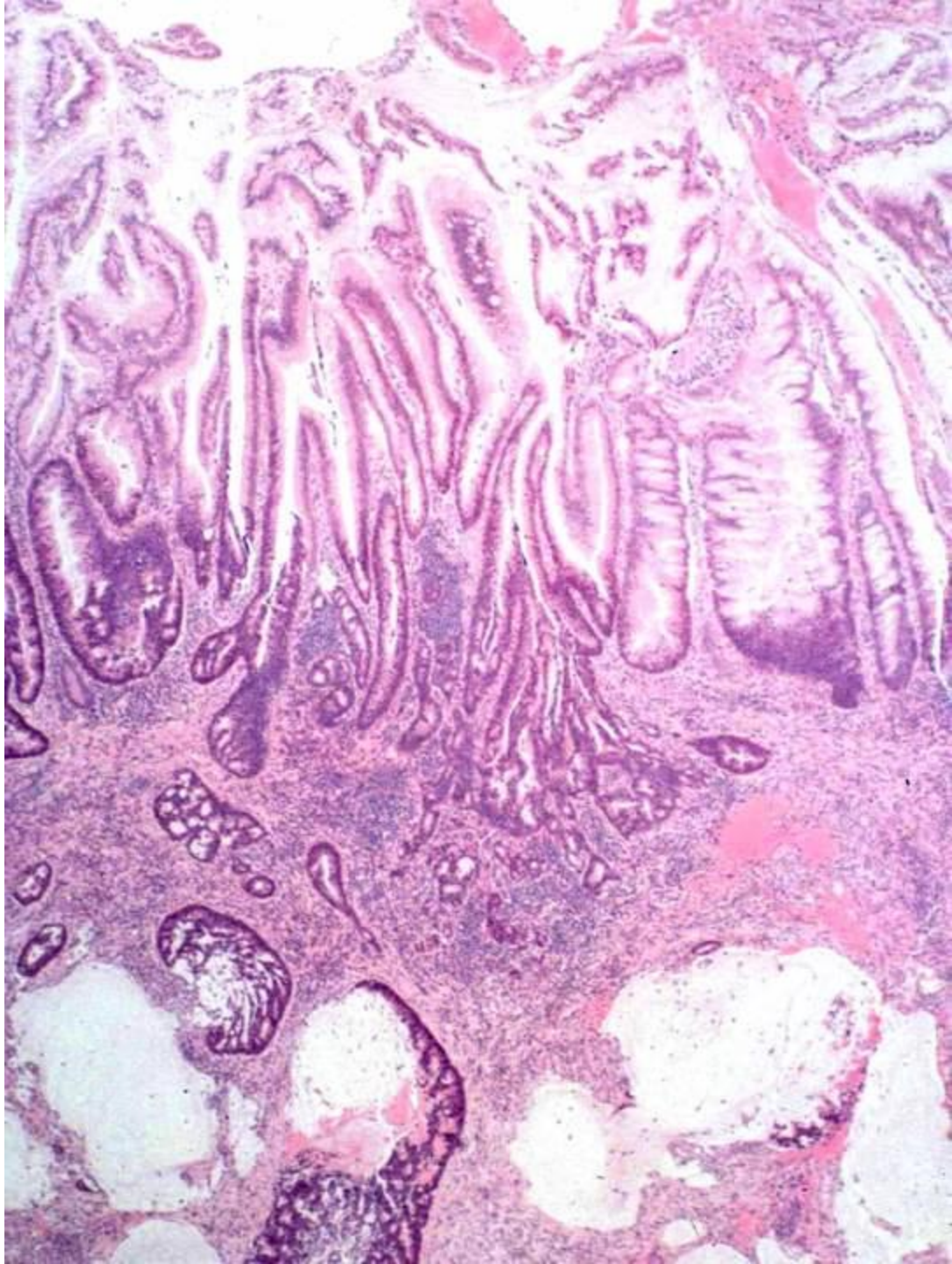
There is an association between appendiceal mucinous neoplasms and diverticula.....

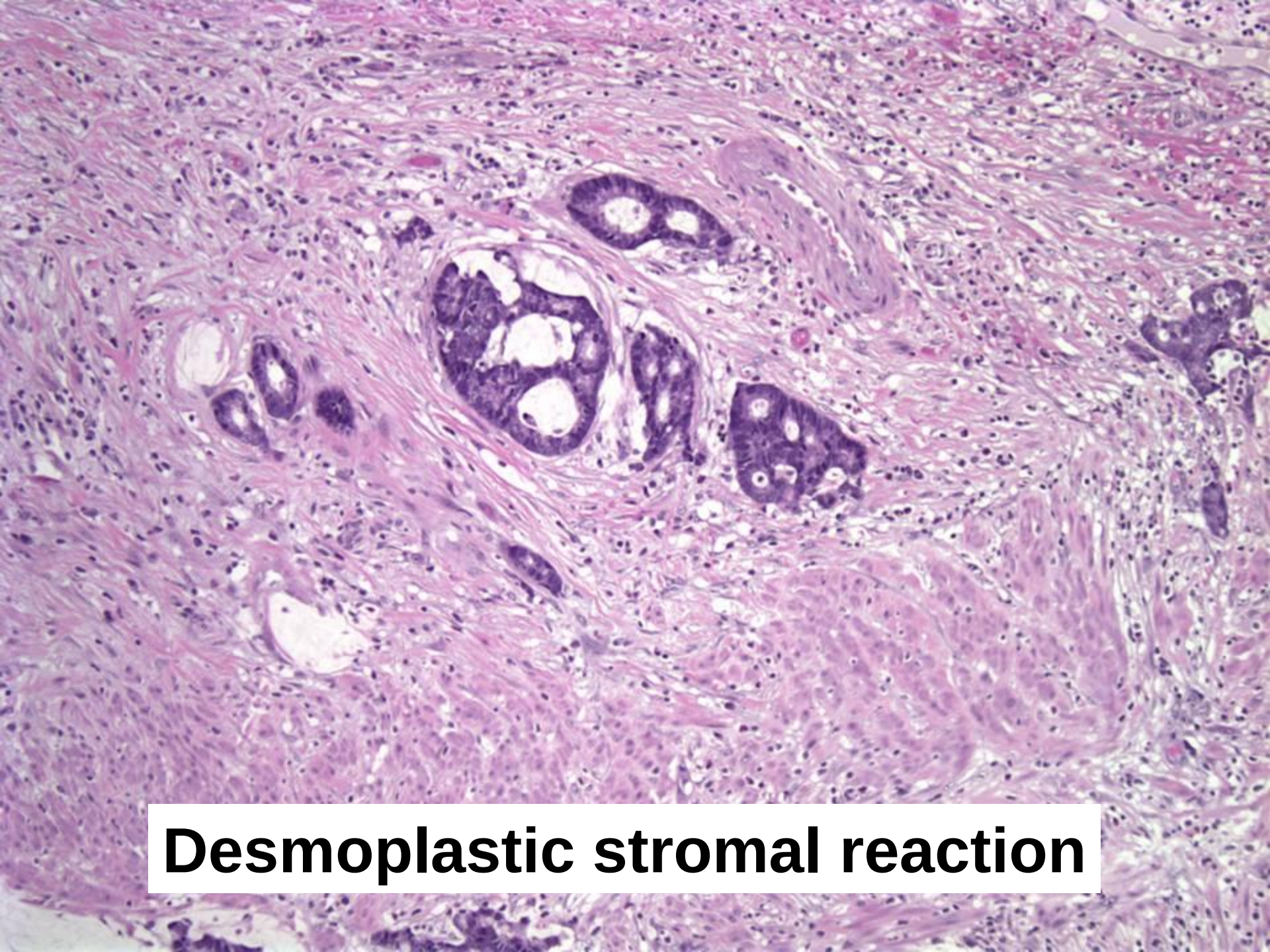
Diverticulum

May rupture and result in spread of mucinous neoplasm to peritoneal surfaces.

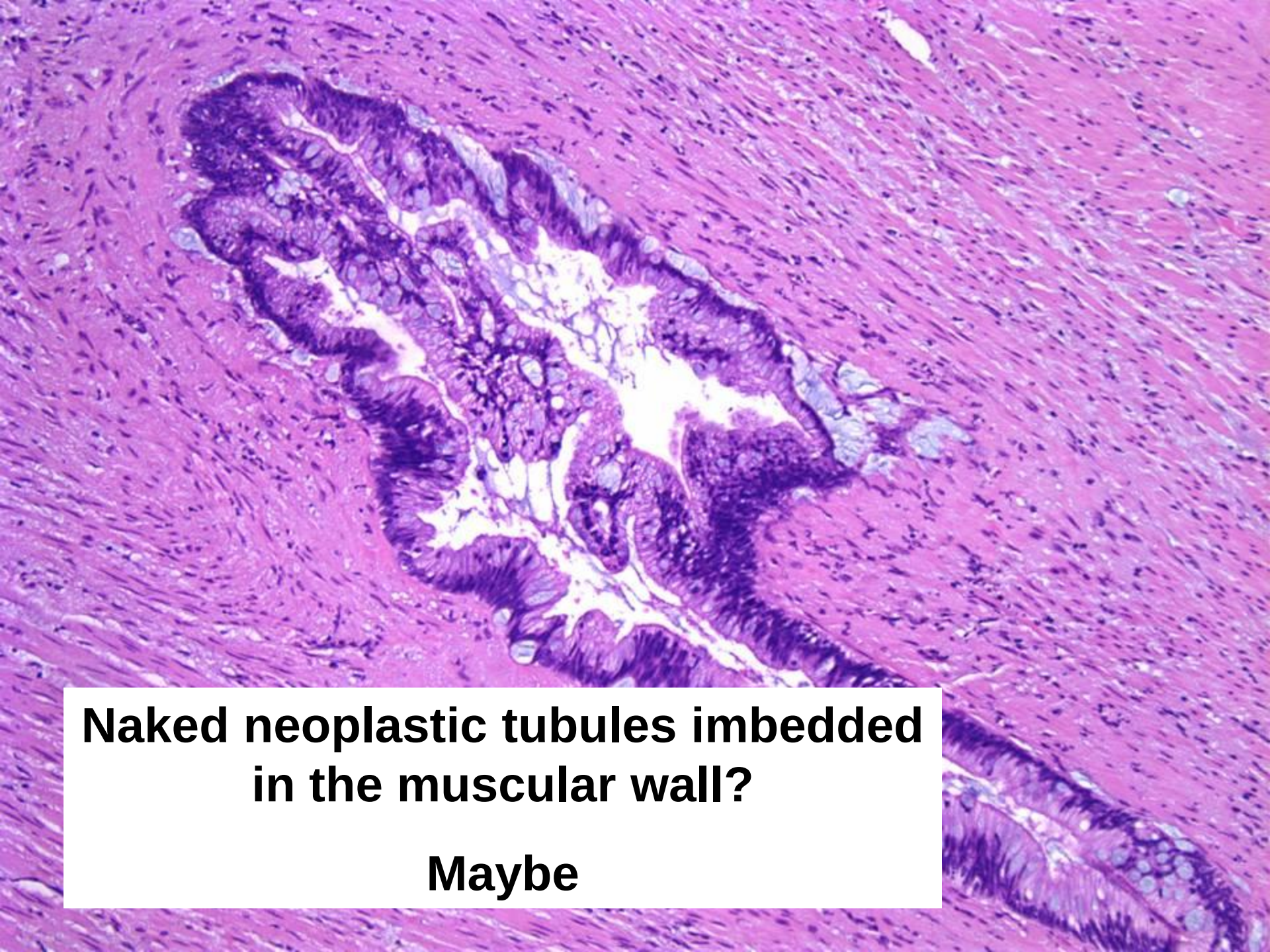


Then how do we recognize invasive carcinoma?




Desmoplastic stromal reaction

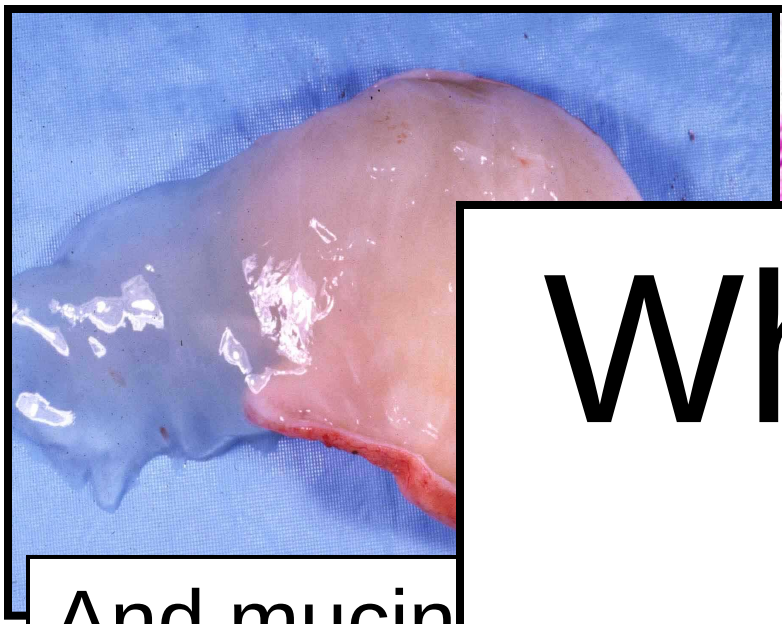

High grade
epithelium floating in
mucin pools



Naked neoplastic tubules imbedded in the muscular wall?

Maybe

The surgeon found:

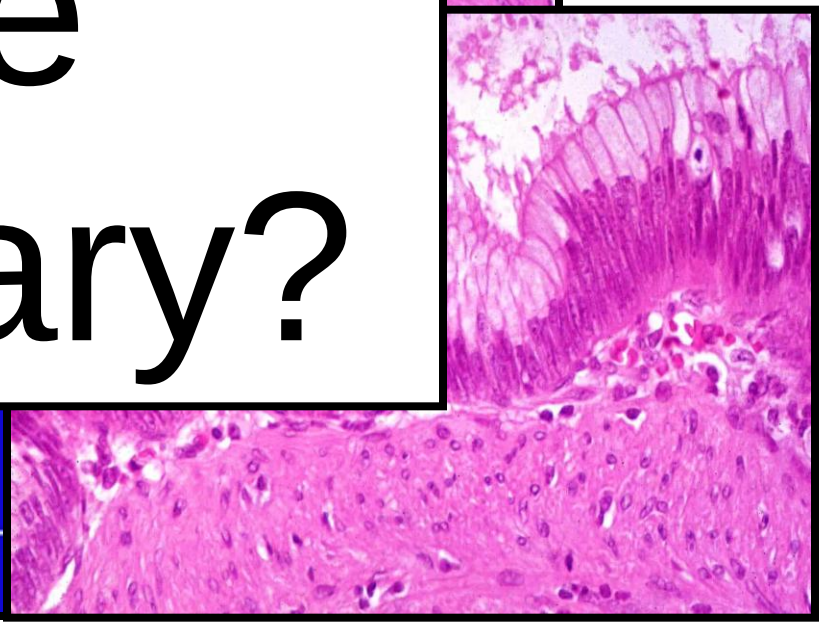


ucinous
oplasm in
ppendix

And mucin

Where is the primary?

Mucinous neoplasm on ovary



Mucinous tumors in both appendix and ovary: which is the primary?

7 studies between 1991 and 1999

Looking at synchronous mucinous tumors of ovary and appendix, many with pseudomyxoma peritonei:

Based on clinicopathologic and immunohistochemical data, all but one conclude that appendix is by far the most common primary site.

Mucinous tumors in both appendix and ovary: which is the primary?

7 studies between 1991 and 1999

Looking at synchronous mucinous tumors of ovary and appendix, many with pseudomyxoma peritonei:

Genetic studies among these confirm that, in almost all cases, these synchronous tumors are the same.

Appendiceal Mucinous Neoplasms—how do they behave?

	#	Epithelium	Peritoneal spread	Survival with peritoneal spread		
				3 year	5 year	10 year
LAMN	88	Low grade	56%	100%	86%	45%
MACA	16	High grade	75%	90%	44%	No data
Discordant	3	LG in app HG in perit	All	No data		

LAMN : low grade appendiceal mucinous neoplasm

But stage is important too:

No pt with LAMN confined to the appendix died.
2 of 3 with LAMN and localized periappendiceal spread died.

What about the peritoneal mucin and epithelium in our case?

Pseudomyxoma peritonei

(literally means 'false mucinous tumor of the peritoneum')

is described as a slowly progressive disease process characterized by copious amounts of mucoid fluid and tumor that, over time, fills the peritoneal cavity.

What happens to patients with Pseudomyxoma Peritonei?

108 of 109 cases with epithelium, not all appendiceal

	Epithelium	App primary	Organ invasion	Nodal Mets	5 yr survival
DPAM (low grade)	Scant, low grade like app adenoma	57% known 43% c/w appendix	12% usually ovary	3%	84%
PMAC (high grade)	Abundant, high grade or carcinoma	40% known 43% colon	97% Intestine Ovary	50%	7%
Indeterminant	Mixed	79%	79%	21%	38%

DPAM: diffuse peritoneal adenomucinosis

PMAC: peritoneal mucinous adenocarcinoma

Ronnett, et al, Am J Surg Pathol, 19:1398, 1995

Conclusions based on these studies:

Low grade appendiceal mucinous neoplasms are likely to stay confined to the appendix, or may spread to peritoneal surfaces. They have a good prognosis.

High grade appendiceal mucinous neoplasms are likely to spread to the peritoneum and have a worse prognosis.

Conclusions based on these studies:

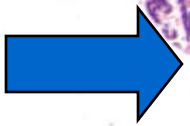
Pseudomyxoma peritonei with scant, low grade epithelium has a good prognosis.

Pseudomyxoma peritonei with abundant, high grade (carcinomatous) epithelium has a bad prognosis.

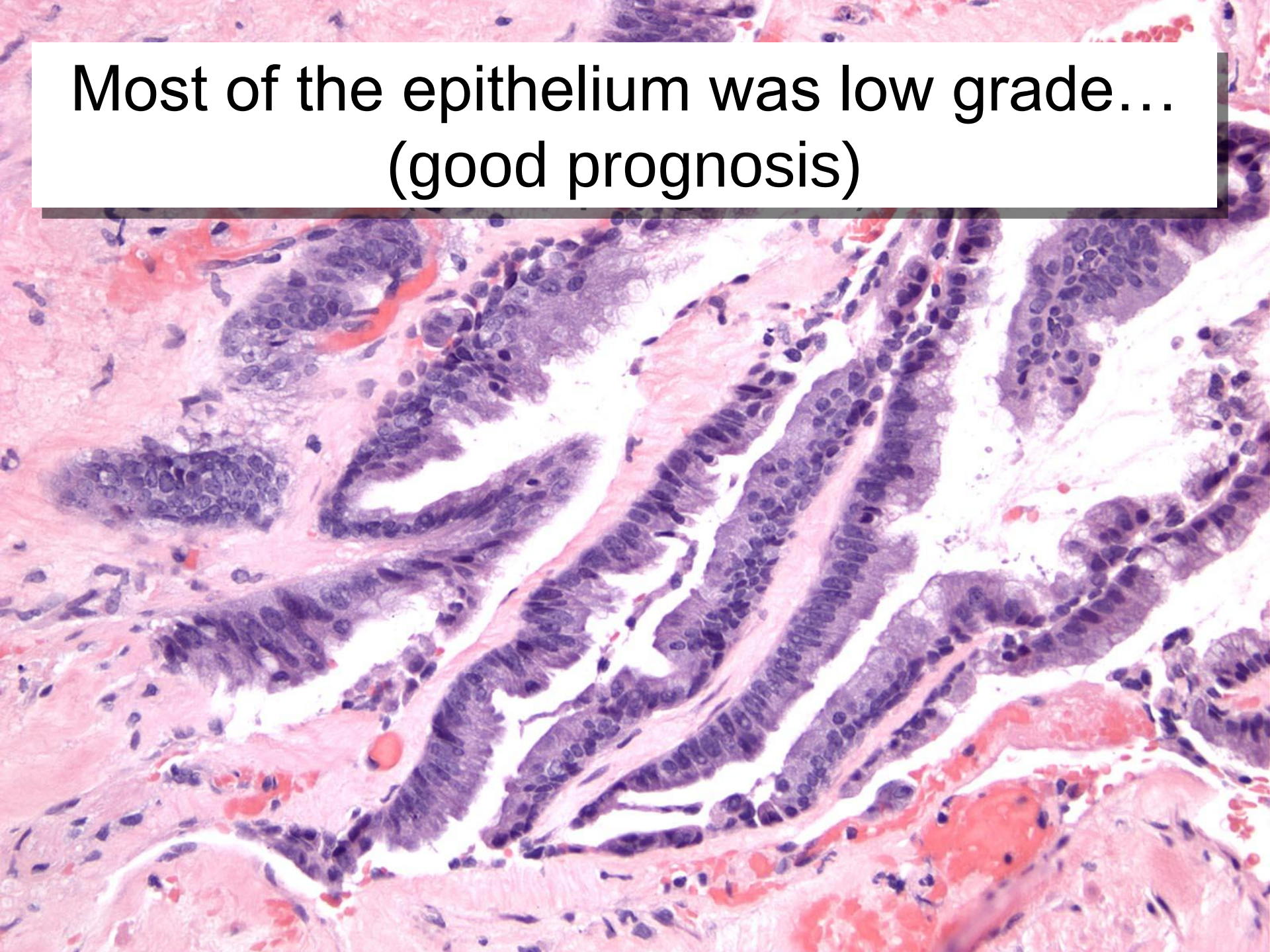
What does this suggest about our case?

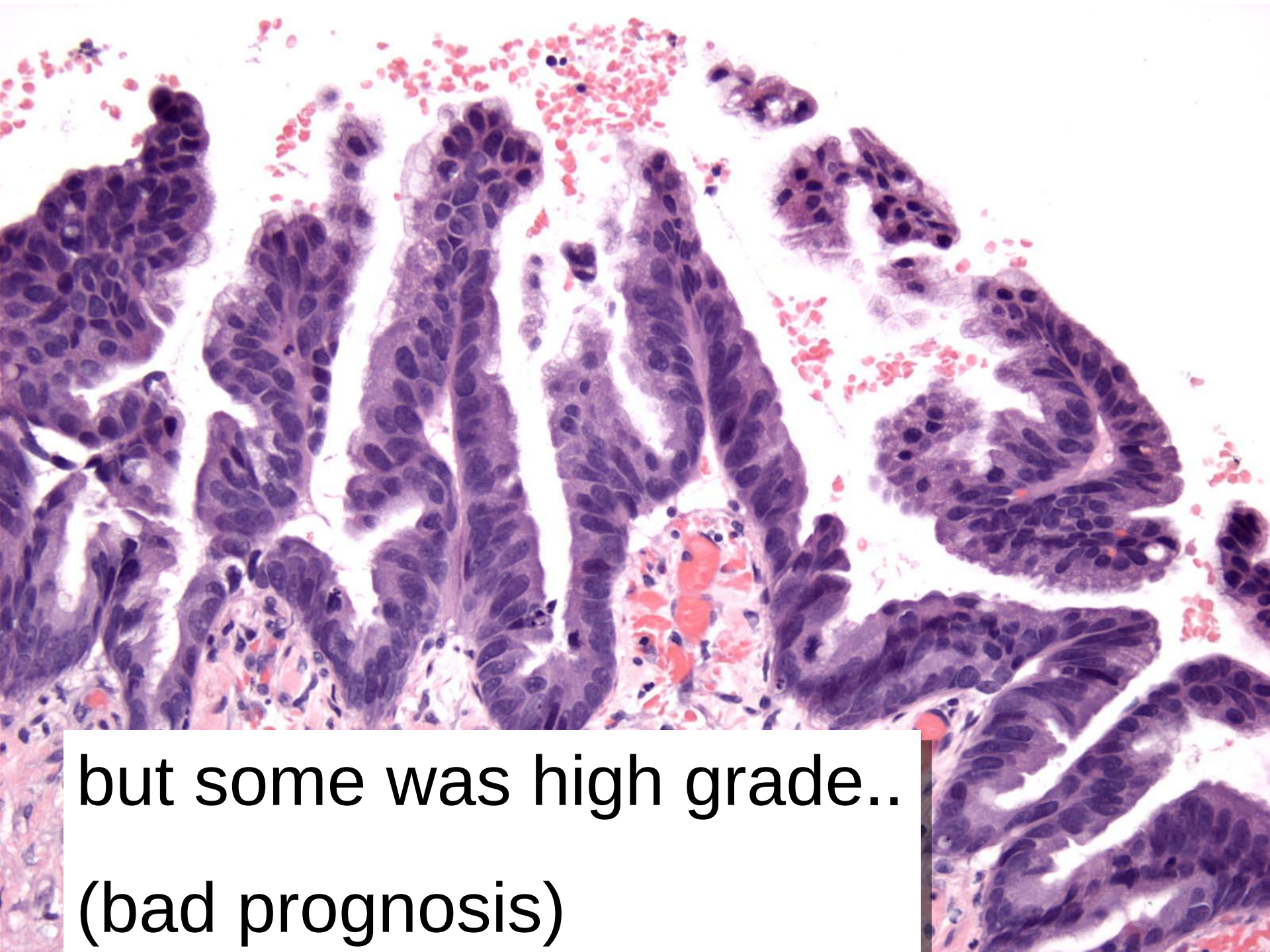
In our case the appendiceal tip was dilated and filled with mucus…

and there was a partial epithelial lining.



Most of the epithelium was low grade…
(good prognosis)



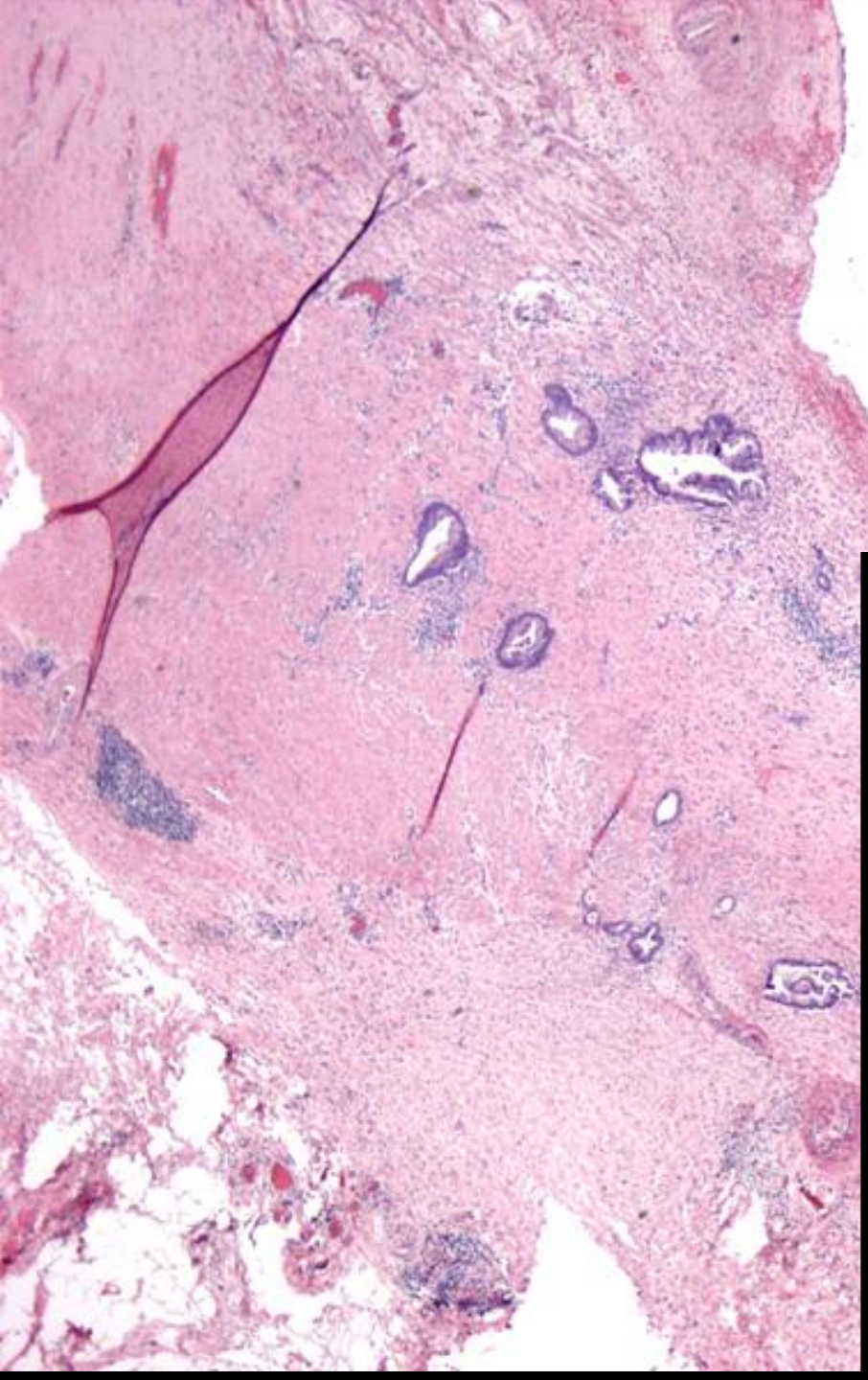


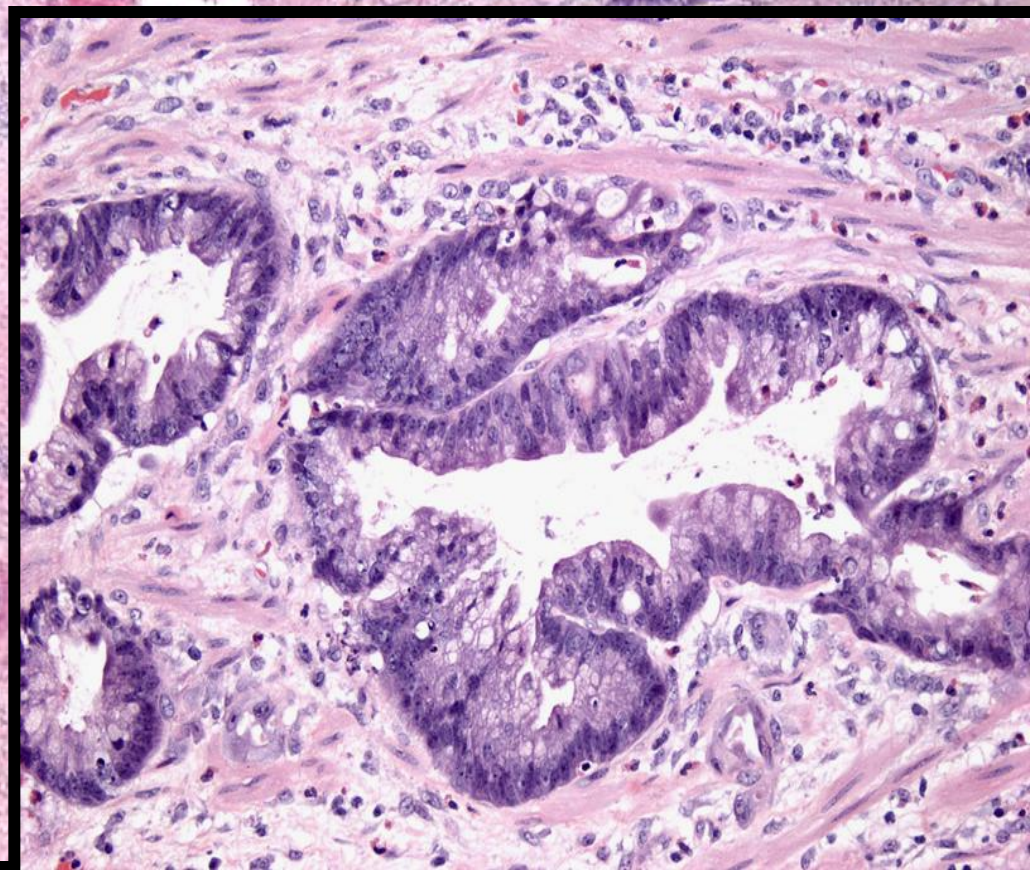
but some was high grade..

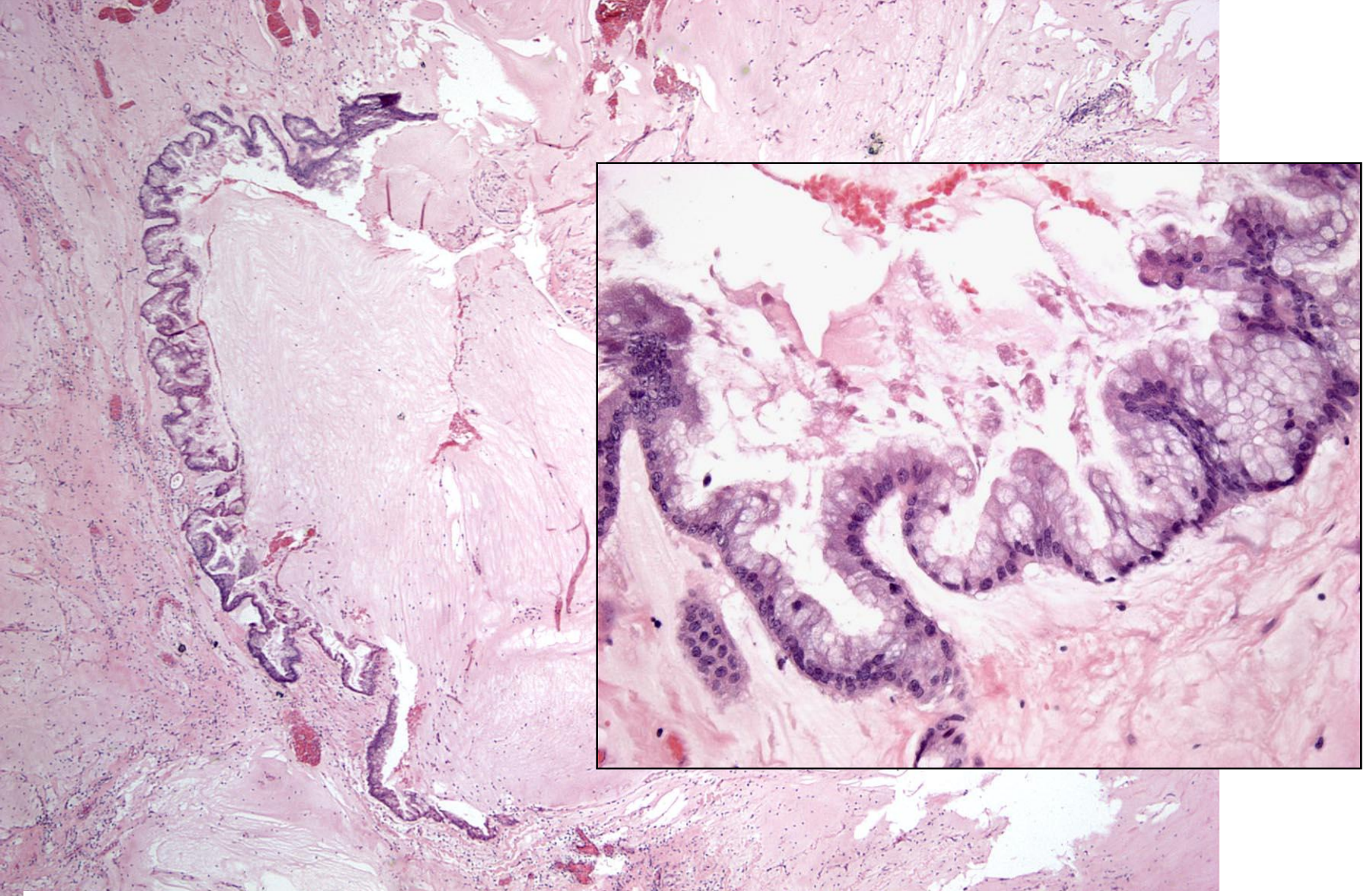
(bad prognosis)

There were invasive tubules in the wall.

(bad prognosis)

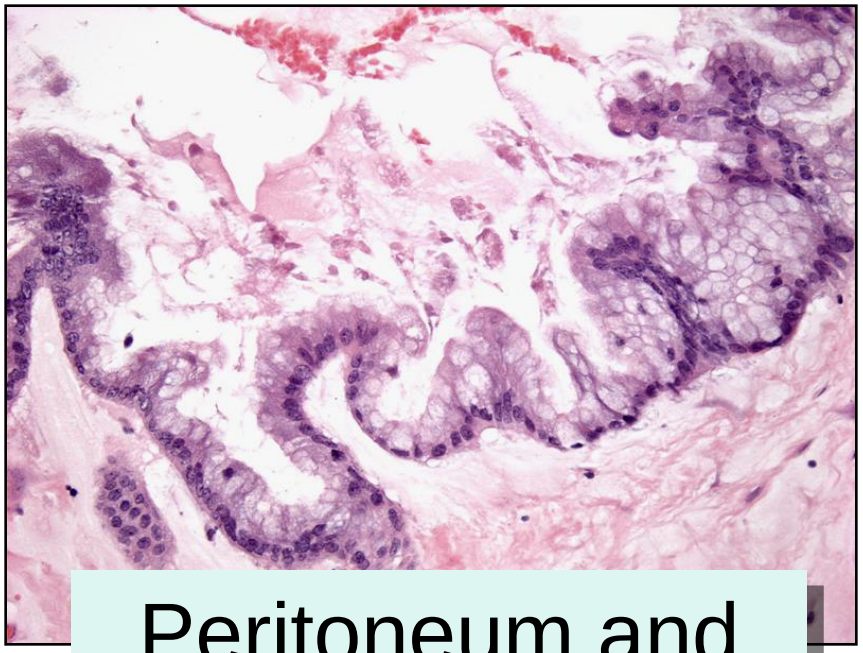




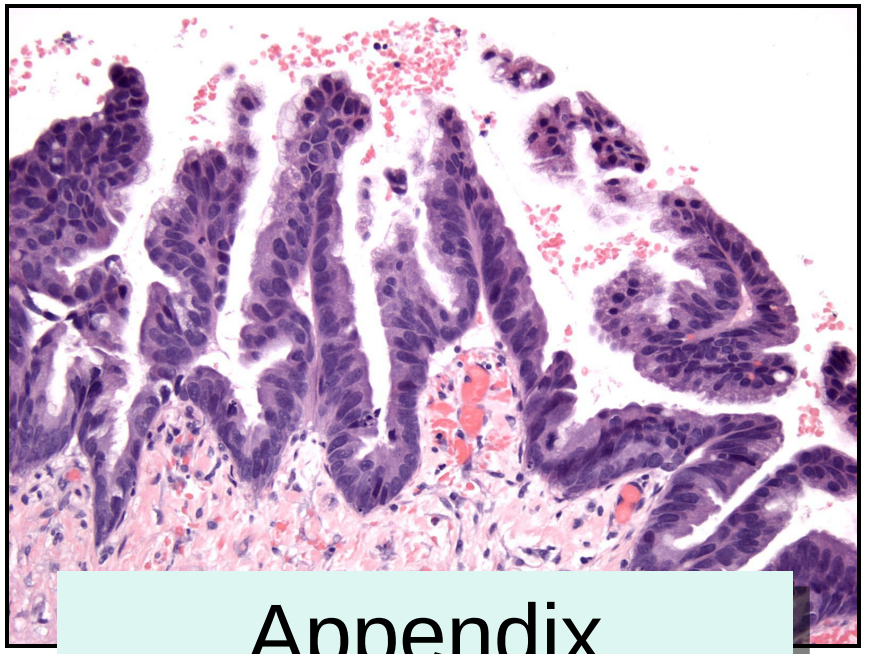


There was also peritoneal mucus with strips of low grade epithelium (a little bad)

Is this a good prognosis or a bad prognosis case?



Peritoneum and appendix



Appendix

This case is giving us mixed messages; the diagnosis will not be simple…

Diagnosis

Appendix, resection: small invasive adenocarcinoma

arising in an appendiceal mucinous mucinous neoplasm/(cystadenoma) with mostly low-grade dysplastic epithelium,

with rupture and localized extra-appendiceal peritoneal mucus containing only low-grade dysplastic epithelium (PMP/pseudomyxoma peritonei) .

(long comment explaining the mixed messages)

The names for this are not standardized.

However, we have considerable information about behavior.

First, the epithelium in the peritoneal mucus is all low grade . The data we have indicates that such epithelium is unlikely to invade other organs or metastasize to lymph nodes, and the 5-year survival after diagnosis is around 85%.

We do not know how the small invasive carcinoma in the appendix modifies this behavior and survival data.

Terminology for neoplastic ***peritoneal*** mucin accumulations

- **Pseudomyxoma peritonei**
- **Disseminated peritoneal adenomucinosis (DPAM) and Peritoneal mucinous carcinomatosis (PMCA)**
- **Mucinous adenoma/ neoplasm of uncertain malignant potential/ neoplasm of uncertain malignant potential/ carcinoma**

Where did the term "Pseudomyxoma peritonei" come from?

- Werth, in 1884, first described pseudomyxoma peritonei as the presence abundant gelatinous material in the peritoneal cavity as a result of perforation of an **ovarian** mucinous cystadenoma.
- Frankel, in 1901, described the association of PMP with a ruptured "mucocele" of the **appendix**.

Pseudomyxoma peritonei
What's wrong with this term?

- The term has been used too broadly, to include low grade appendiceal neoplasm, neoplasms from other sites, and also mucinous carcinomas.
- It does not sufficiently describe the findings.

Solution:

Invent new terms!

DPAM and PMCA
Disseminated peritoneal adenomucinosis
Peritoneal mucinous carcinomatosis

- Ronnett and colleagues classified 109 cases of multifocal peritoneal mucinous tumors according to a set of criteria….

Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to “pseudomyxoma peritonei.” AJSP 1995;19(12):1390-1408

DPAM

disseminated peritoneal adenomucinosis

“A clinicopathologic entity characterized by mucinous ascites and noninvasive mucinous implants with a characteristic distribution and containing histologically benign mucinous epithelium derived from an appendiceal mucinous adenoma and having an indolent course.”

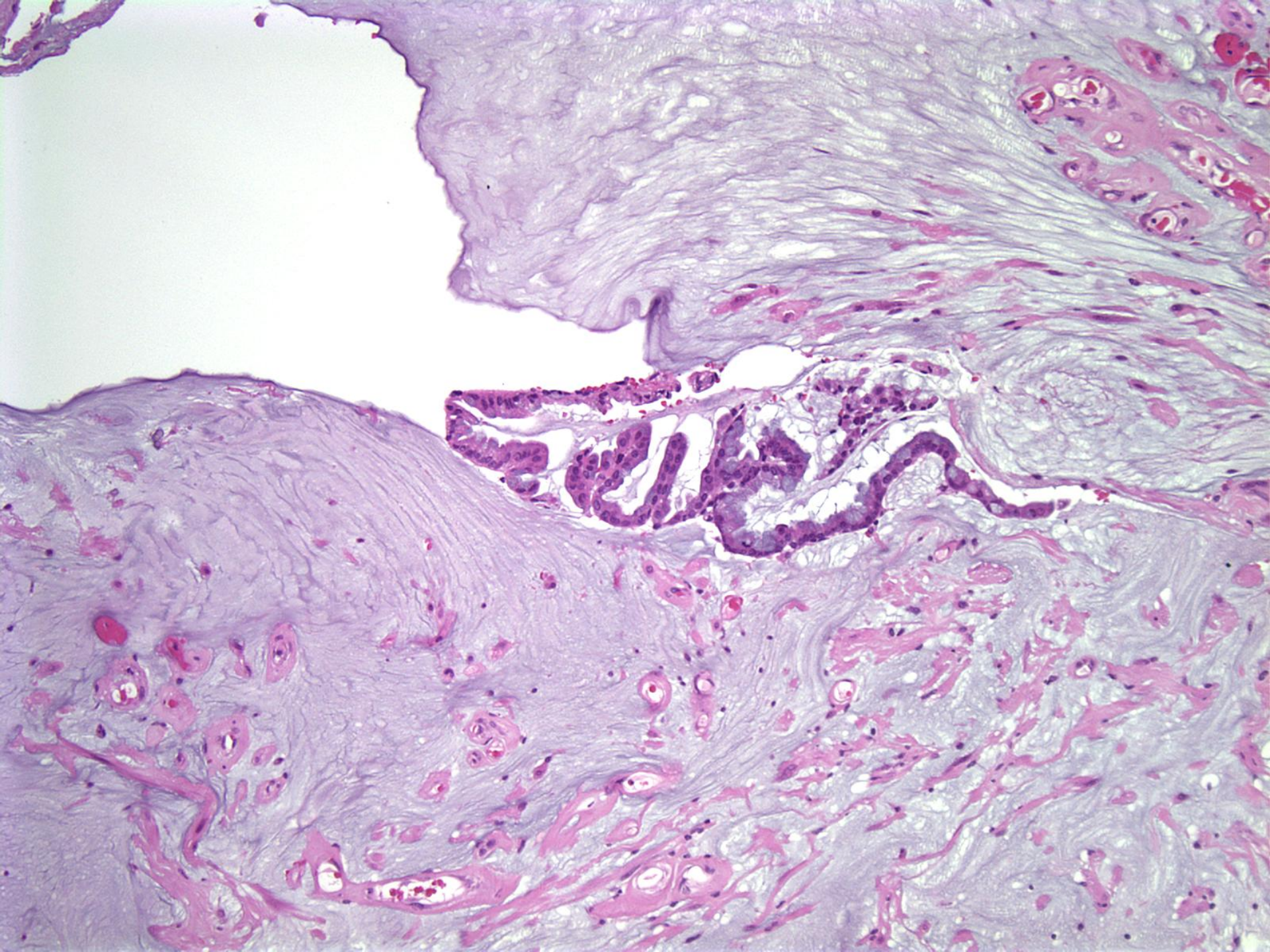
DPAM
disseminated peritoneal adenomucinosis

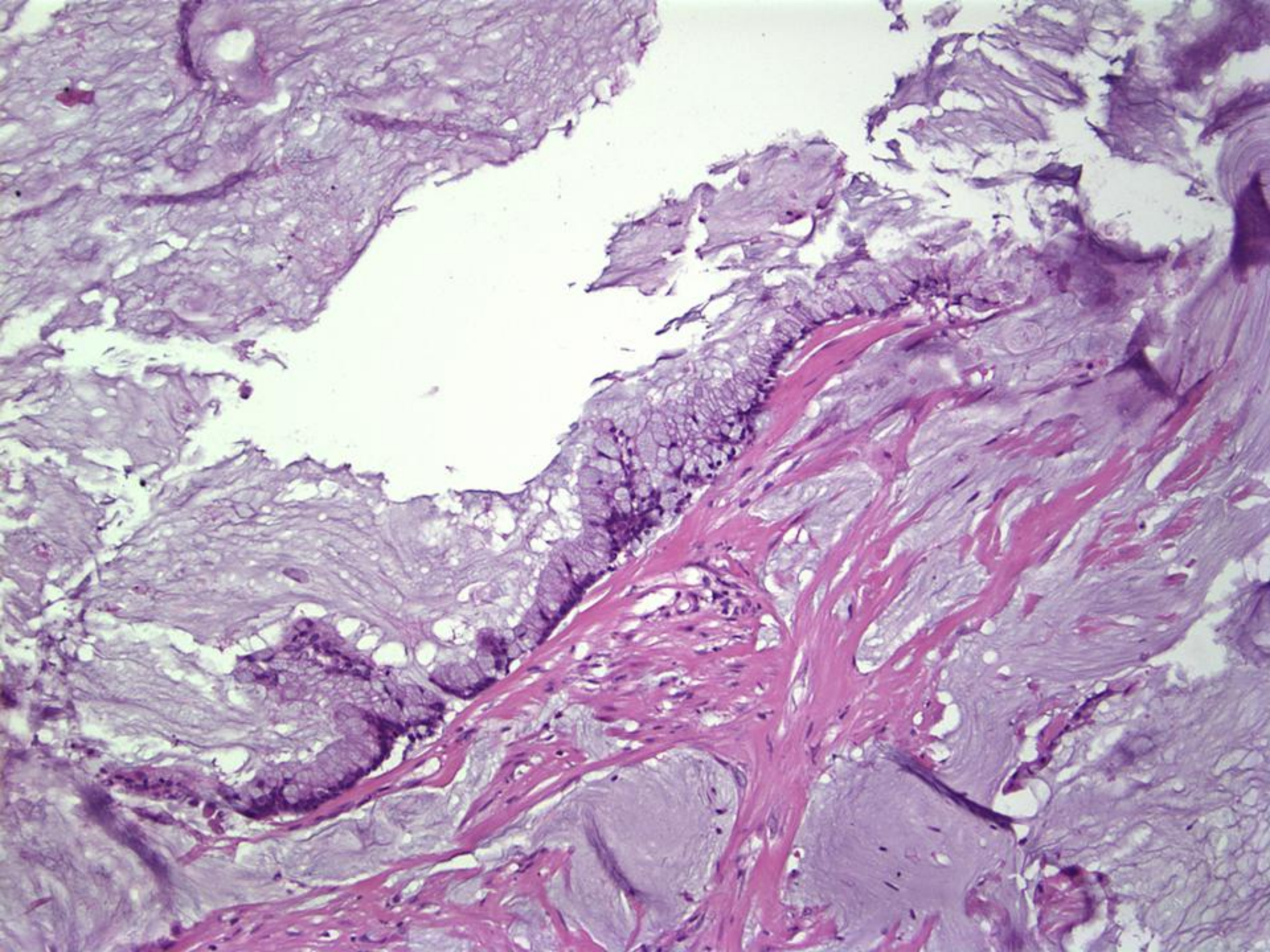
Peritoneal mucin

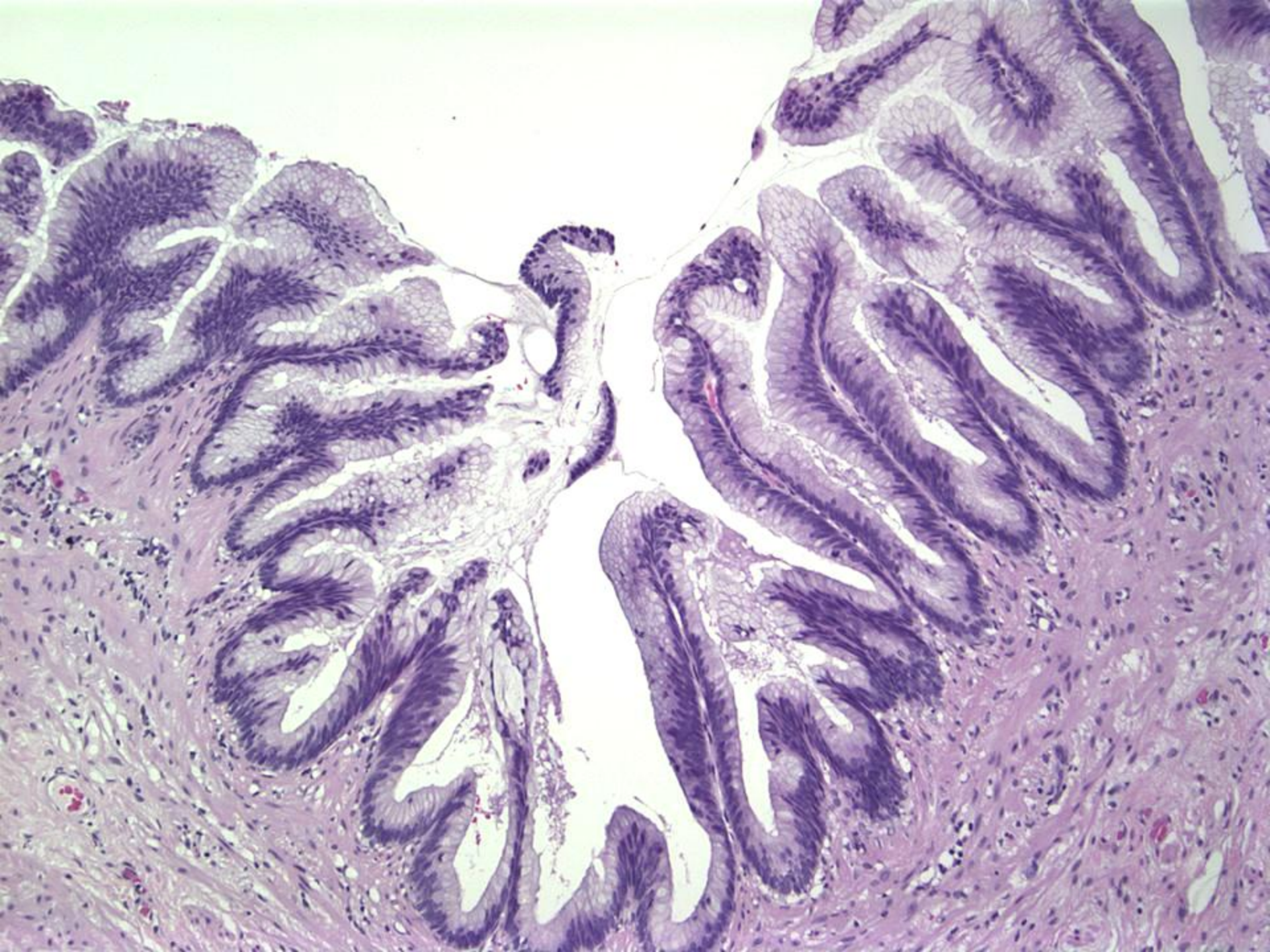
Low grade epithelium

Noninvasive implants

Appendiceal adenoma







PMCA

Peritoneal mucinous carcinomatosis

“cases with <u>histologically malignant</u> peritoneal tumors derived from appendiceal or intestinal mucinous carcinomas”

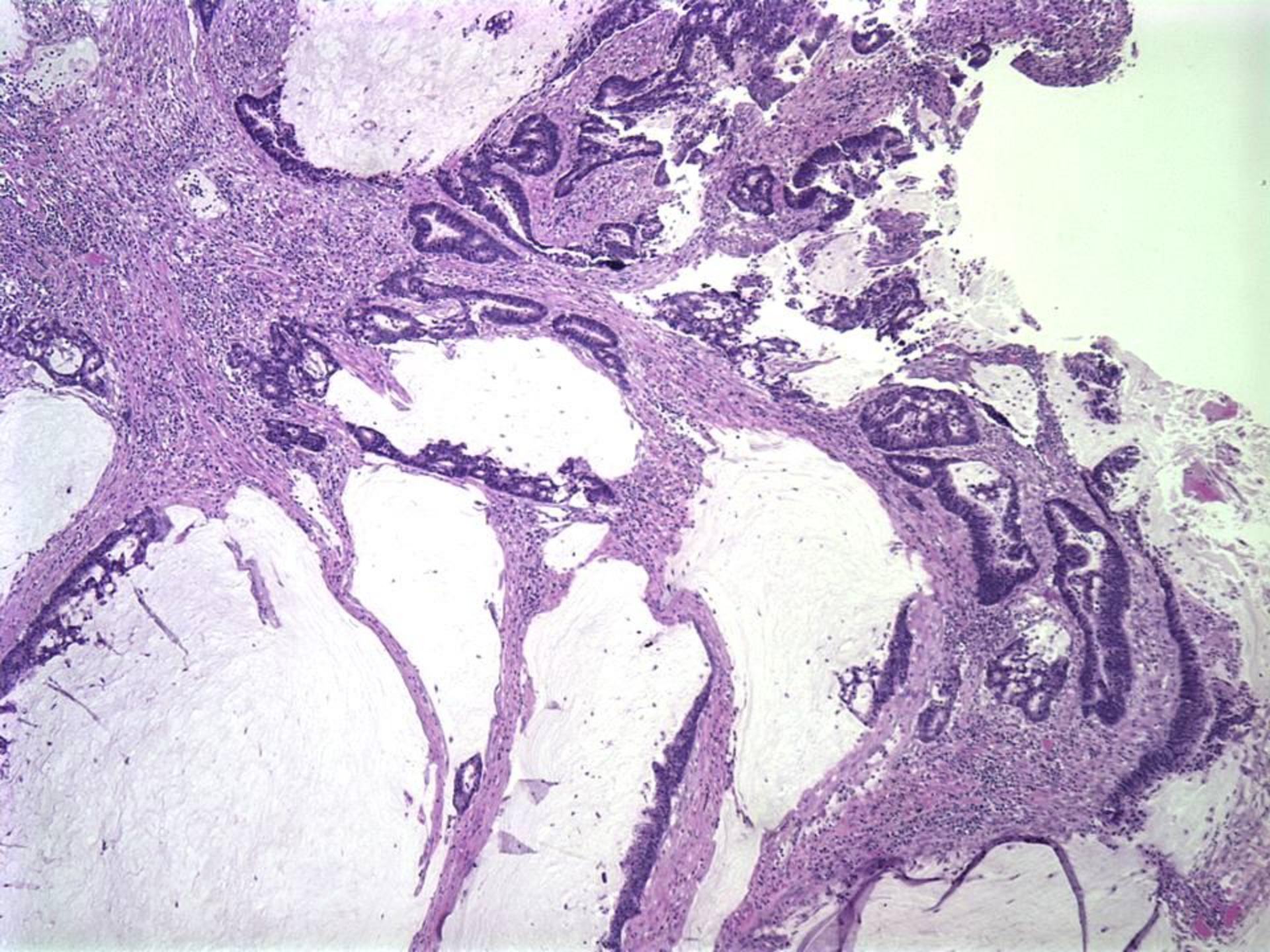
PMCA
Peritoneal mucinous carcinomatosis

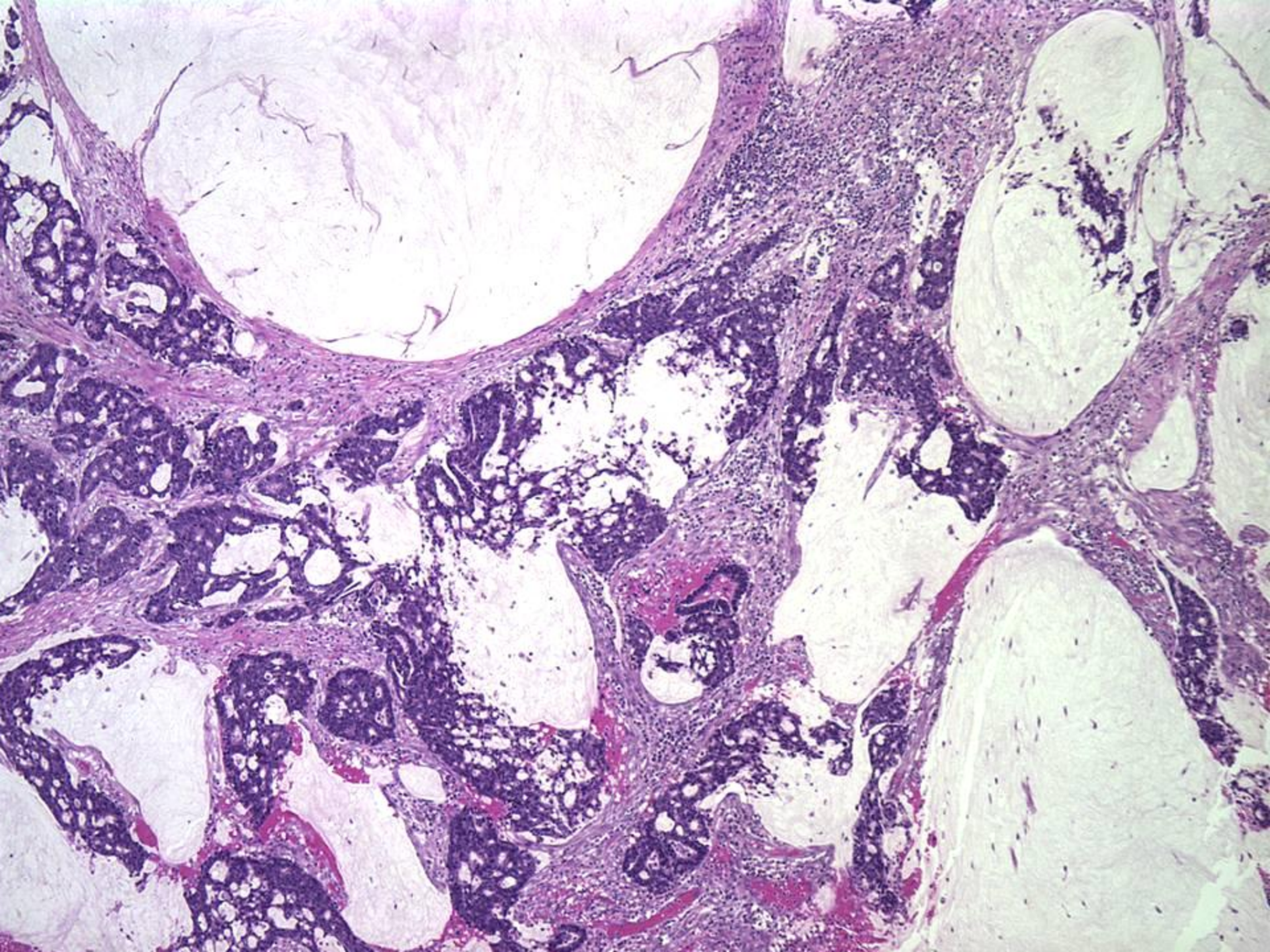
Peritoneal mucin

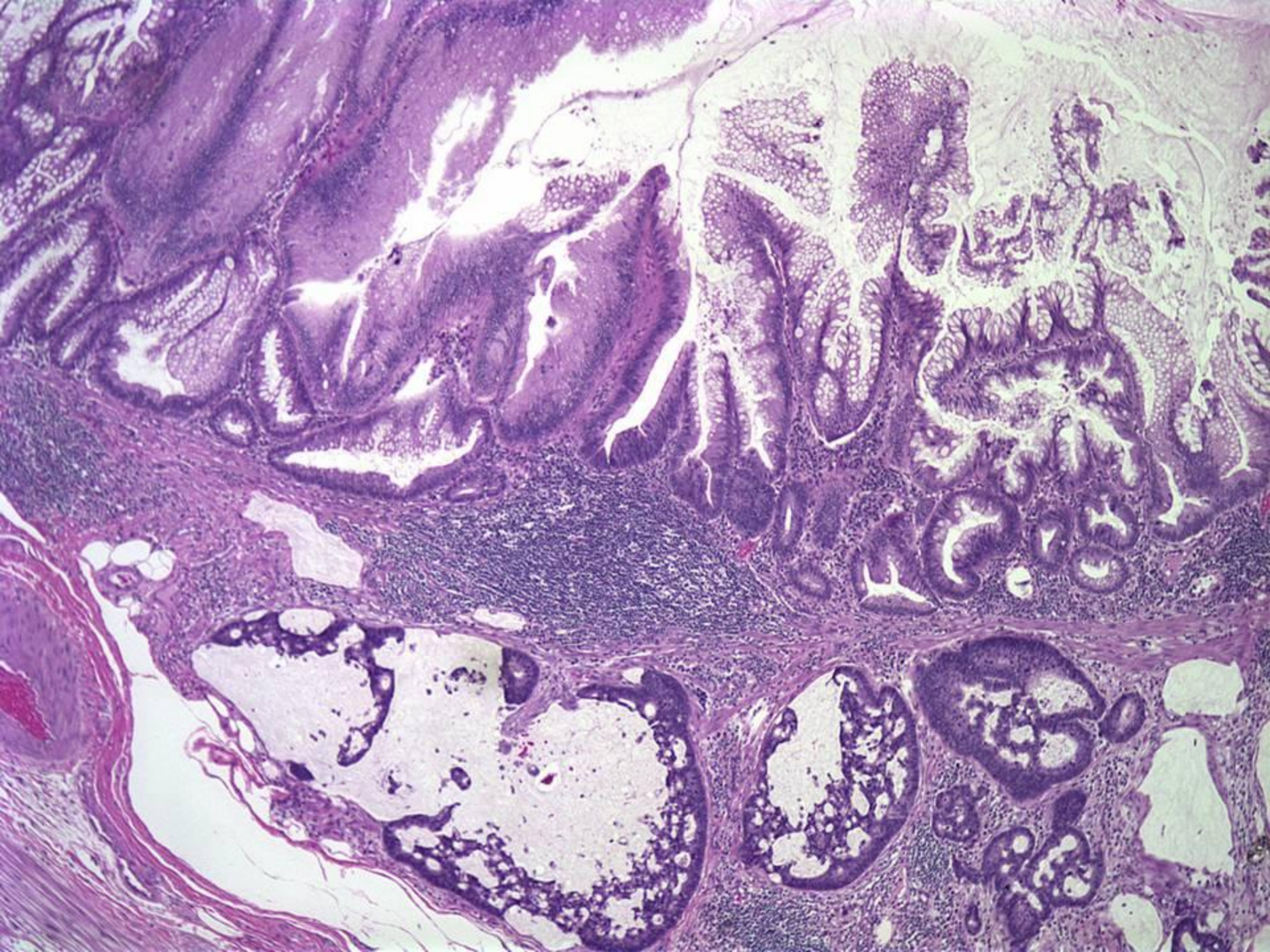
High grade (carcinomatous) epithelium

Invasion

Appendiceal or intestinal mucinous adenocarcinoma







DPAM—65 cases

8 parenchymal organ invasion

7 ovary

1 bowel wall

2 lymph node involvement

1 extra-abdominal disease

84% age-adjusted 5 year survival

PMCA—30 cases

29 parenchymal organ invasion

11 ovary, 17 bowel wall, 4 liver, 1 uterus

15 lymph node involvement

0 extra-abdominal disease

6.7% age-adjusted 5 year survival

Terminology akin to that for ovarian surface epithelial tumors

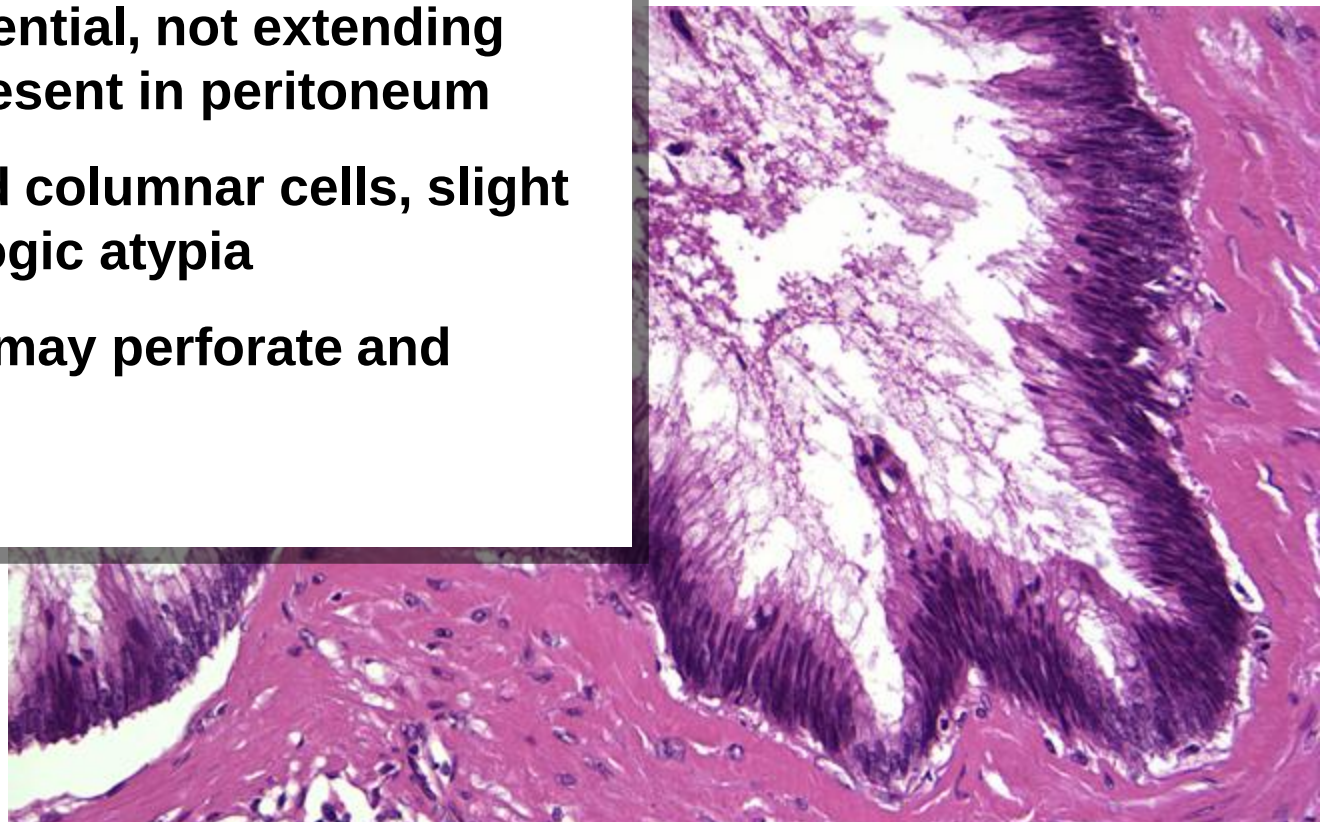
Mucinous adenoma

Sessile, circumferential, not extending through wall or present in peritoneum

Simple to stratified columnar cells, slight to moderate cytologic atypia

Appendix dilated, may perforate and extravasate mucin

Clinically benign



Pai RK, Longacre TA. Appendiceal mucinous tumors and pseudomyxoma peritonei. Histologic features, diagnostic problems, and proposed classification. Adv Anat Pathol 2005;12:291-311

Terminology akin to that for ovarian surface epithelial tumors

Mucinous neoplasm of uncertain malignant potential

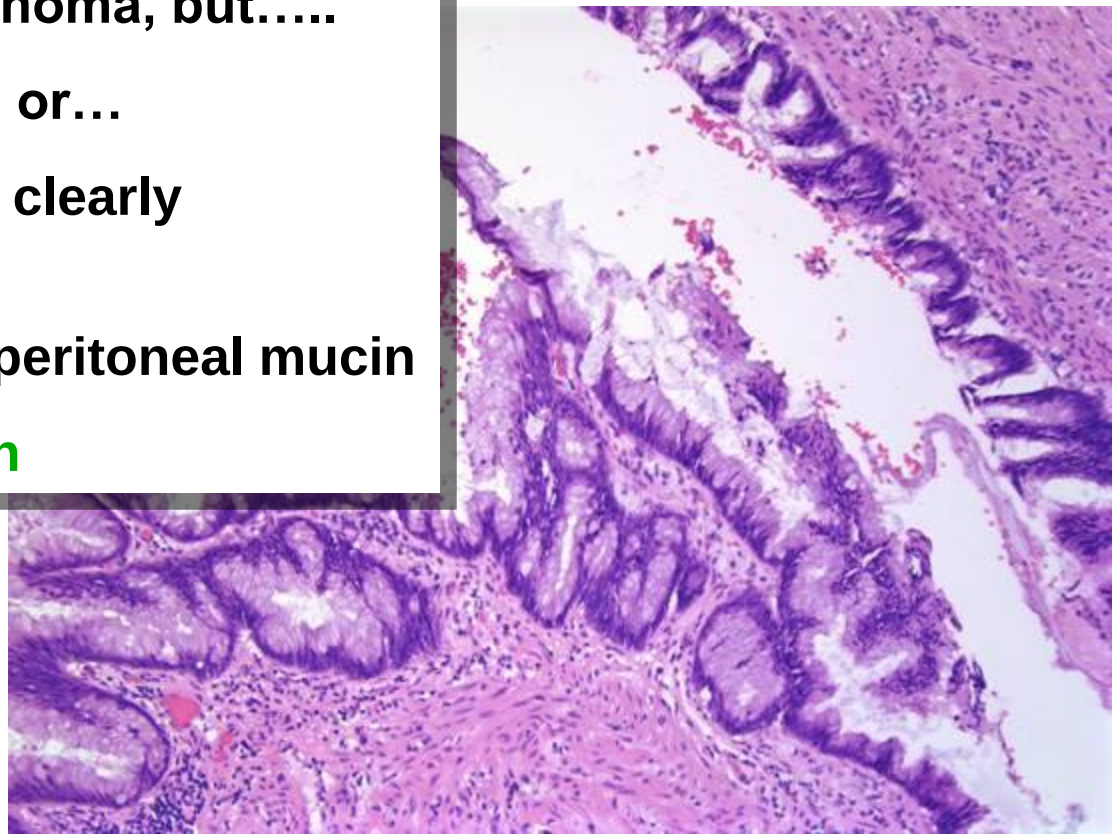
Features of mucinous adenoma, but…..

Proximal margin involved, or…

Epithelium in wall, but not clearly invasive, or…

Uncertain if epithelium in peritoneal mucin

Clinical behavior uncertain



Terminology akin to that for ovarian surface epithelial tumors

Mucinous neoplasm of low malignant potential

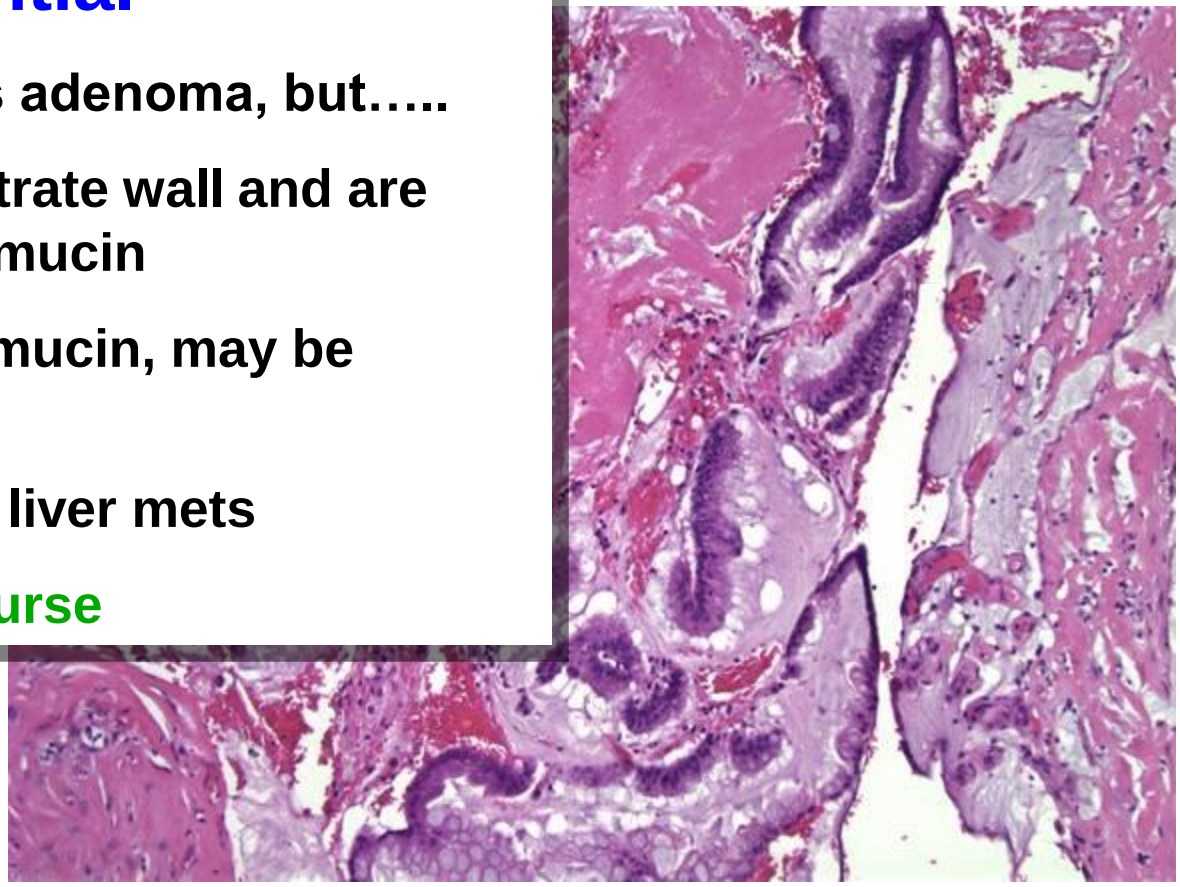
Features of mucinous adenoma, but…..

Neoplastic cells penetrate wall and are present in peritoneal mucin

Abundant peritoneal mucin, may be extensive, but….

No lymph node, lung, liver mets

Protracted clinical course



Terminology akin to that for ovarian surface epithelial tumors

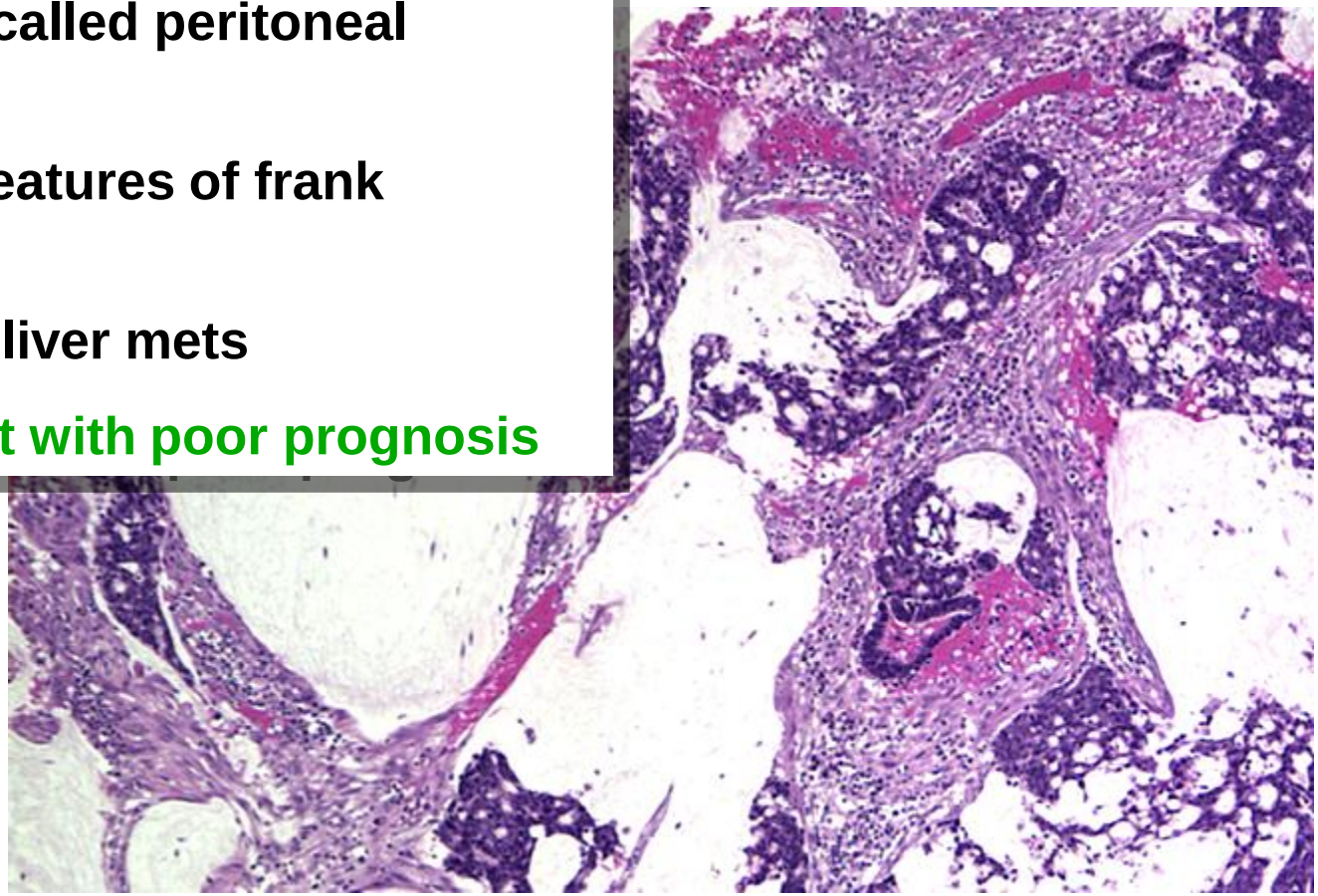
Mucinous adenocarcinoma

Infrequently associated with PMP—when present should be called peritoneal carcinomatosis

Cytoarchitectural features of frank carcinoma

Lymph node, lung, liver mets

Clinically malignant with poor prognosis



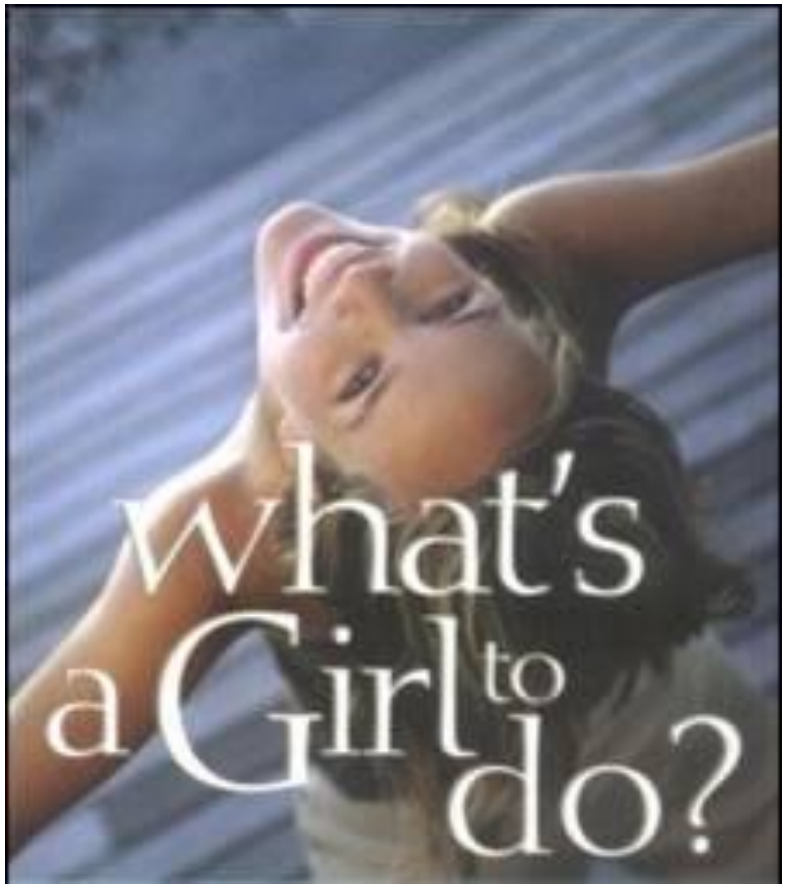
DPAM

PMCA

MNUMP

MNLMP

PMP



Peritoneal mucin accumulations with low grade epithelium are primarily treated surgically, often followed by various types of chemotherapy…

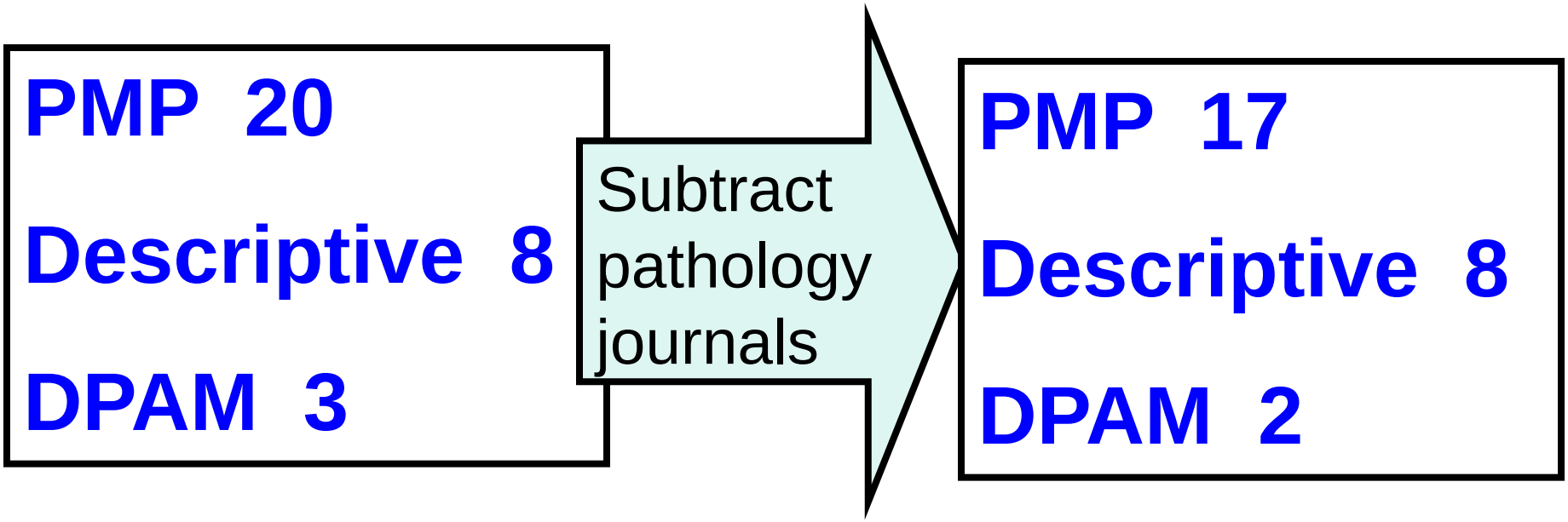
So, what language do the surgeons understand?

PubMed search using terms

Appendiceal mucinous neoplasms peritoneal

Peritoneal adenomucinosis

Looking for the diagnostic terms used in article titles……



My conclusion:
(yours may be different)

- Tell them exactly what is there **descriptively**
  - Grade of neoplasm in appendix
  - Grade of epithelium in peritoneal mucin
- The term **pseudomyxoma peritonei** should appear somewhere in the report for low grade lesions, since that is what the surgeons call it.
- The term **carcinoma** or **carcinomatosis** should appear for high grade (carcinomatous) cases

Terminology

- Low-grade appendiceal mucinous neoplasm (mucinous cystadenoma)
- Low-grade appendiceal mucinous neoplasm with extra-appendiceal spread with report including the term pseudomyxoma peritonei
- Adenocarcinoma arising in association with low-grade appendiceal mucinous neoplasm with report including the term pseudomyxoma peritonei

The 2010 WHO

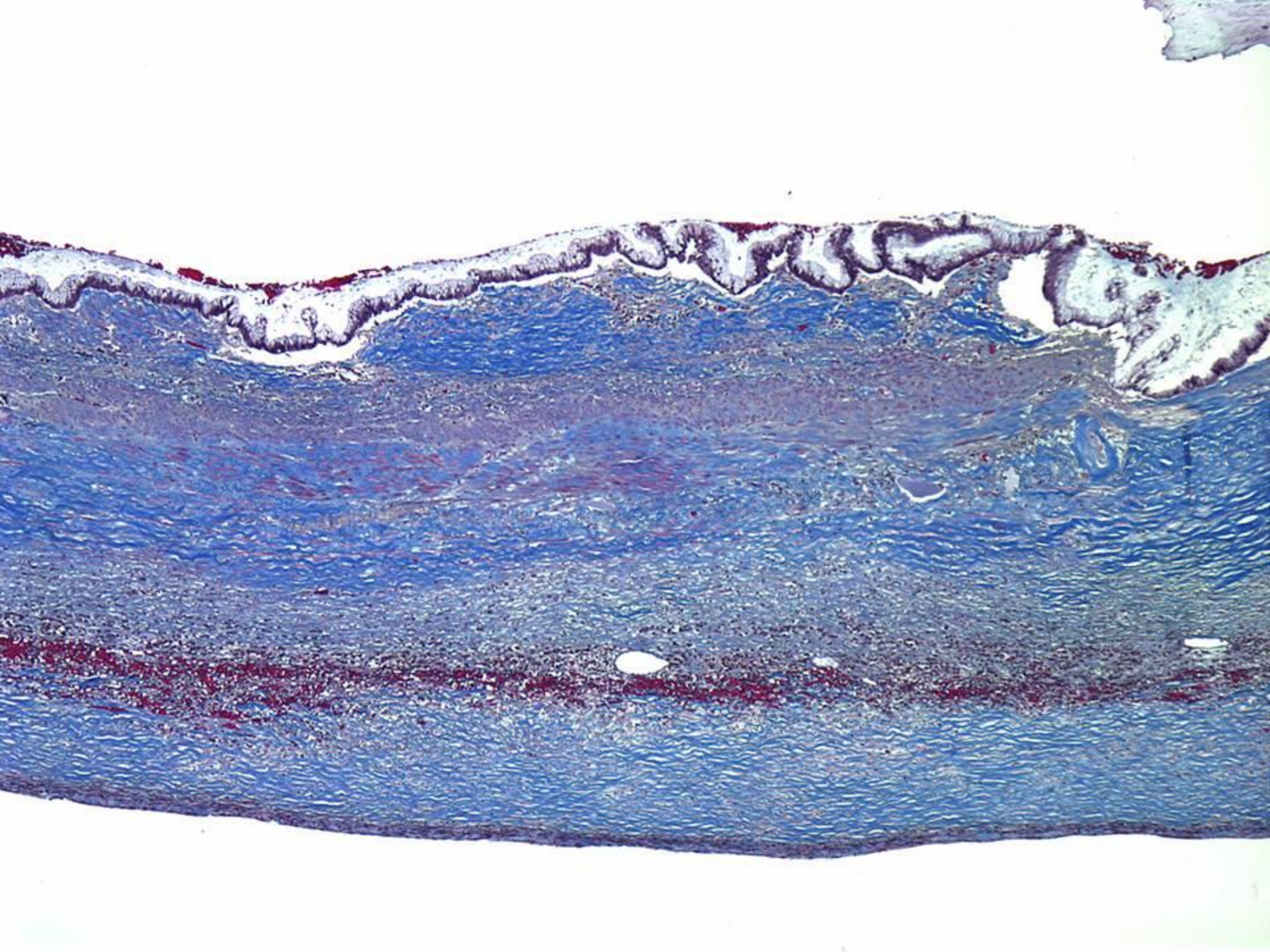
- DID NOT like the term "DPAM/disseminated peritoneal adenomucinosis" because it confuses surgeons

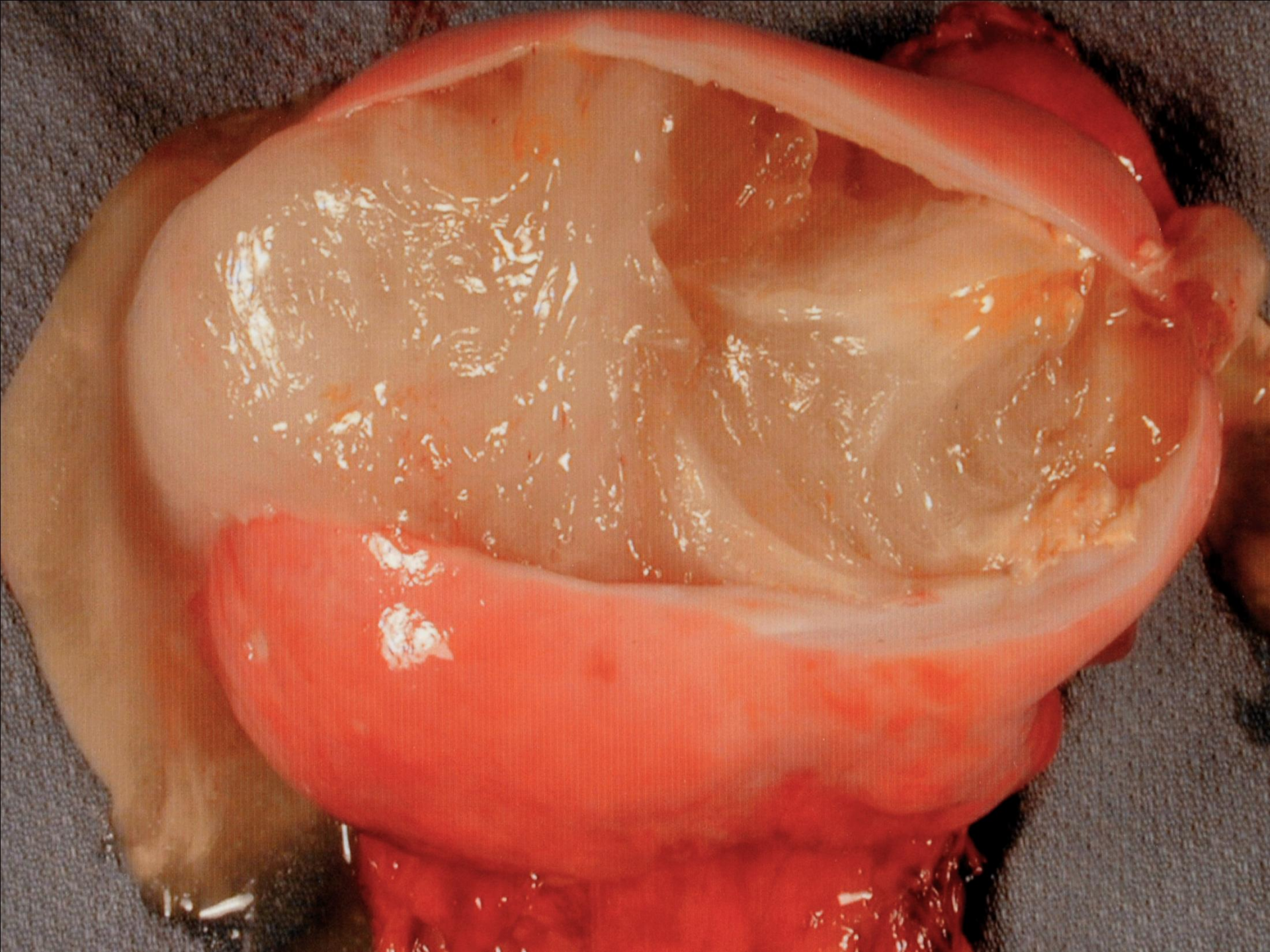
What if ?

- There is only low grade epithelium in the appendix but there is ACELLULAR mucin outside the appendix???

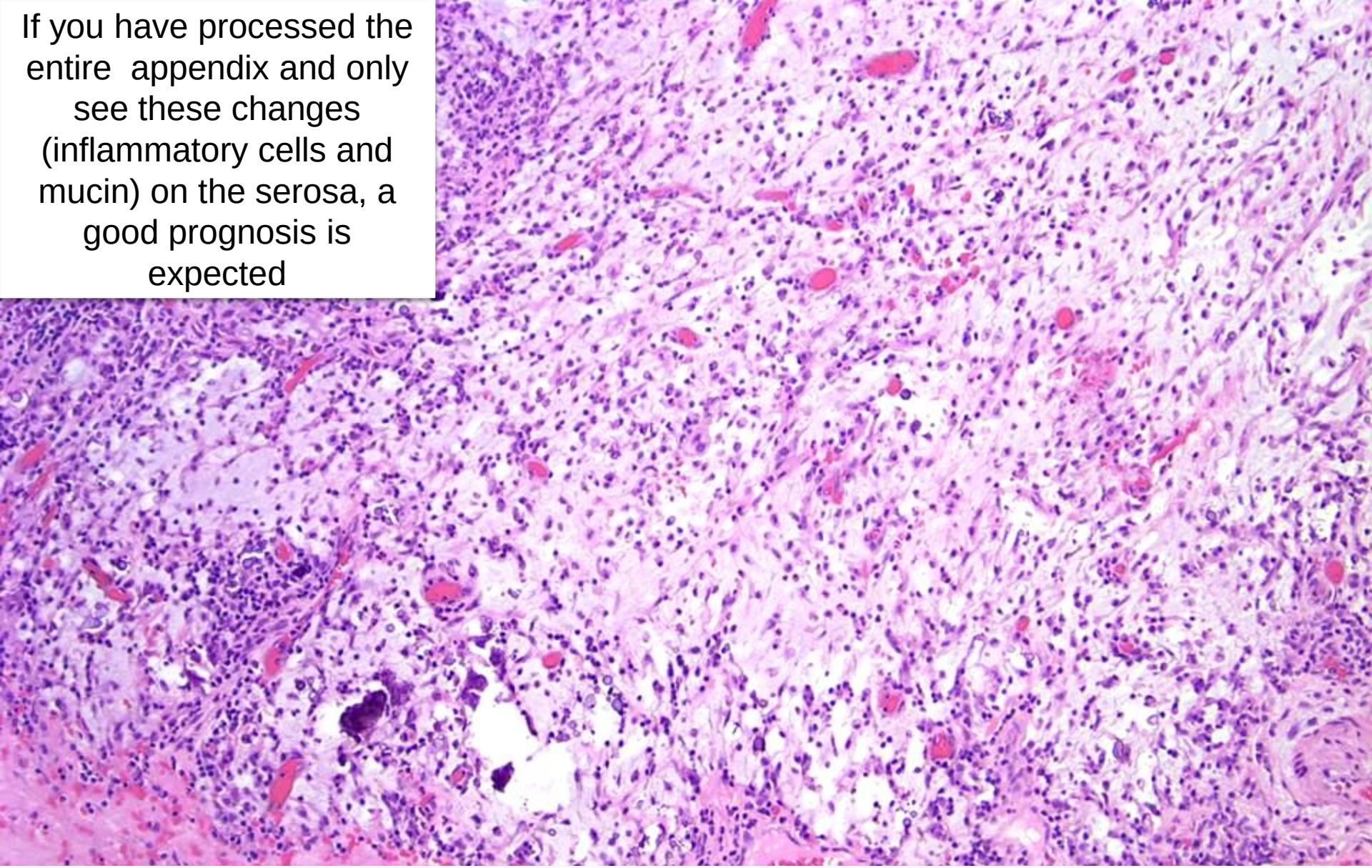
???

- The patient will have an excellent prognosis
- BE SURE TO SAMPLE THE ENTIRE APPENDIX FOR HISTOLOGY
- ALWAYS INK THE WHOLE OUTSIDE FIRST – IT CAN BE DIFFICULT TO TELL WHAT IS INSIDE VERSUS OUTSIDE THE LUMEN WHEN THE WALL IS SCLEROTIC





If you have processed the entire appendix and only see these changes (inflammatory cells and mucin) on the serosa, a good prognosis is expected



Yantiss RK, Shia J, Klimstra DS, Hahn HP, Odze RD, Misdraji J. Prognostic significance of localized extra-appendiceal mucin deposition in appendiceal mucinous neoplasms. Am J Surg Pathol. 2009 Feb;33(2):248-55.

How are appendiceal mucinous neoplasms treated?

Mucinous neoplasm without extra-appendiceal spread

Pseudomyxoma peritonei (low grade epithelium)

DPAM

An intact mucocele (dilated appendix filled with mucin due to mucinous neoplasm) is a benign disorder.

- Keep “mucocele” intact during removal—open laparotomy—examine for pseudomyxoma
- Right hemicolectomy has historically been recommended, but may not be needed unless:
  - Lymph nodal metastases are present (frozen section)
  - Adenoma involves appendiceal margin (frozen section)

Pseudomyxoma peritonei

DPAM

Particular characteristics important to management

- Low grade, noninvasive—may survive 10 years without specialized treatment
- Progression generally confined to peritoneal space
- Patients die from loss of intestinal function due to tumor in abdomen and pelvis
- Rare lymph nodal and/or liver metastases

Pseudomyxoma peritonei

Particular characteristics important to management

- Spare the small bowel early in course—peristalsis?
- Propensity for tumor to deposit in certain locations:
  - Undersurfaces of diaphragms, Right subhepatic space
  - Splenic hilus
  - Abdominal gutters, Pelvis, Cul-de-sac

Pseudomyxoma peritonei/DPAM and PMAC approaches

- Controversial—different approaches and definitions
- Removal of most or all tumor surgically and chemotherapy

Pseudomyxoma peritonei/DPAM and PMAC

What is resected in various surgical approaches?

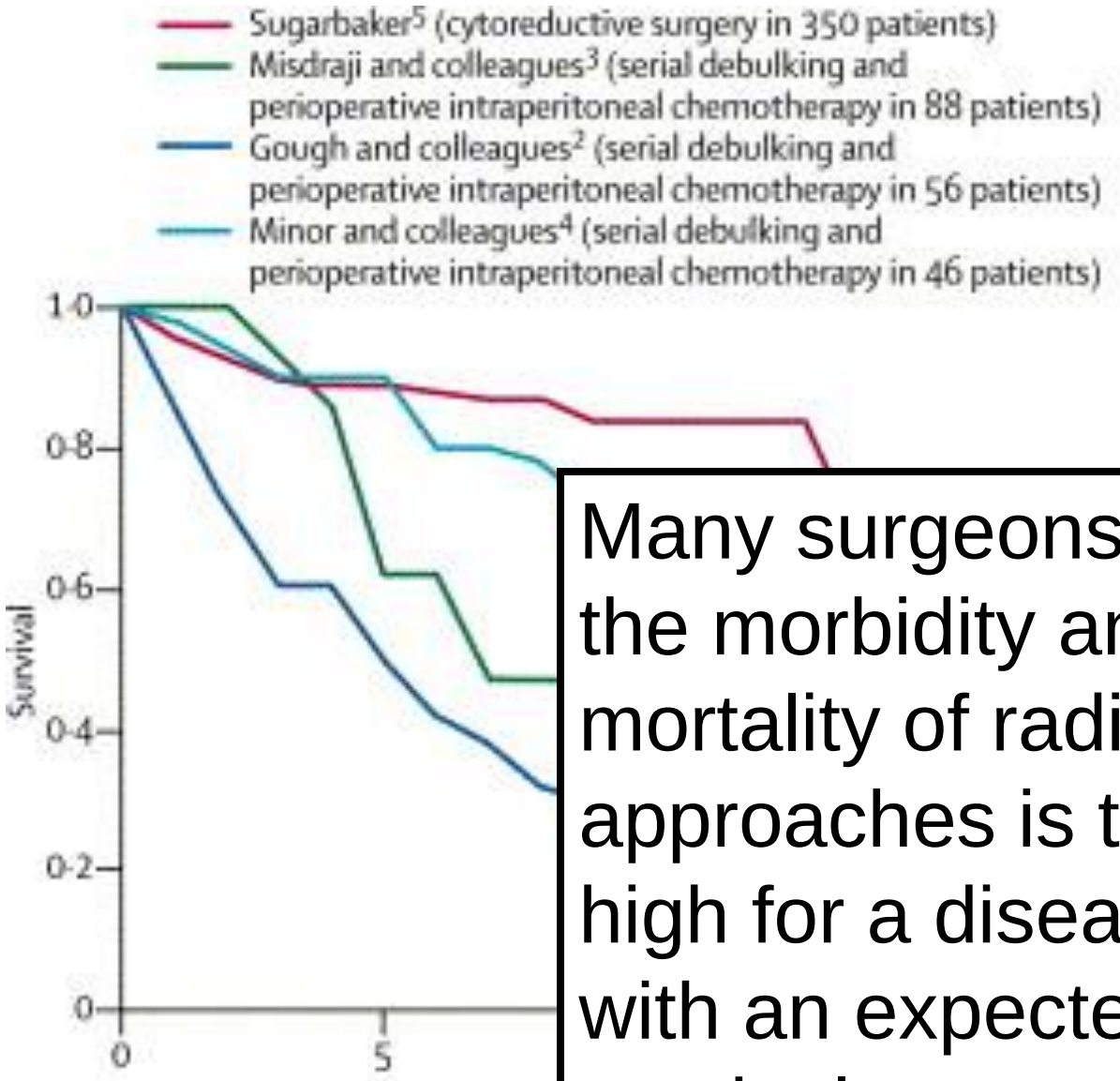
- **Debulking: right hemicolectomy, bilateral oophorectomy, omentectomy, as much of gross disease as possible**
- **Radical cytoreduction: above plus-- spleen, gallbladder, greater and lesser omentum, stripping of peritoneum from pelvis, diaphragm, surface of liver, TAH-BSO, rectum resection in some**
  - **Higher morbidity/mortality**

Perioperative intraperitoneal chemotherapy

- Peritoneal space washed with heated mitomycin solution
- For some patients, postoperative fluorouracil infused

Outcomes for debulking and cytoreduction?

- Differ by institution, study set of patients, grades of neoplasm
- For low grade (DPAM): 5 year survivals range from 67-85%
- For high grade (PMAC): 5 year survivals in the range of 20%



Many surgeons feel the morbidity and mortality of radical approaches is too high for a disease with an expected long survival.

Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? Lancet Oncol 2006;7:69-76

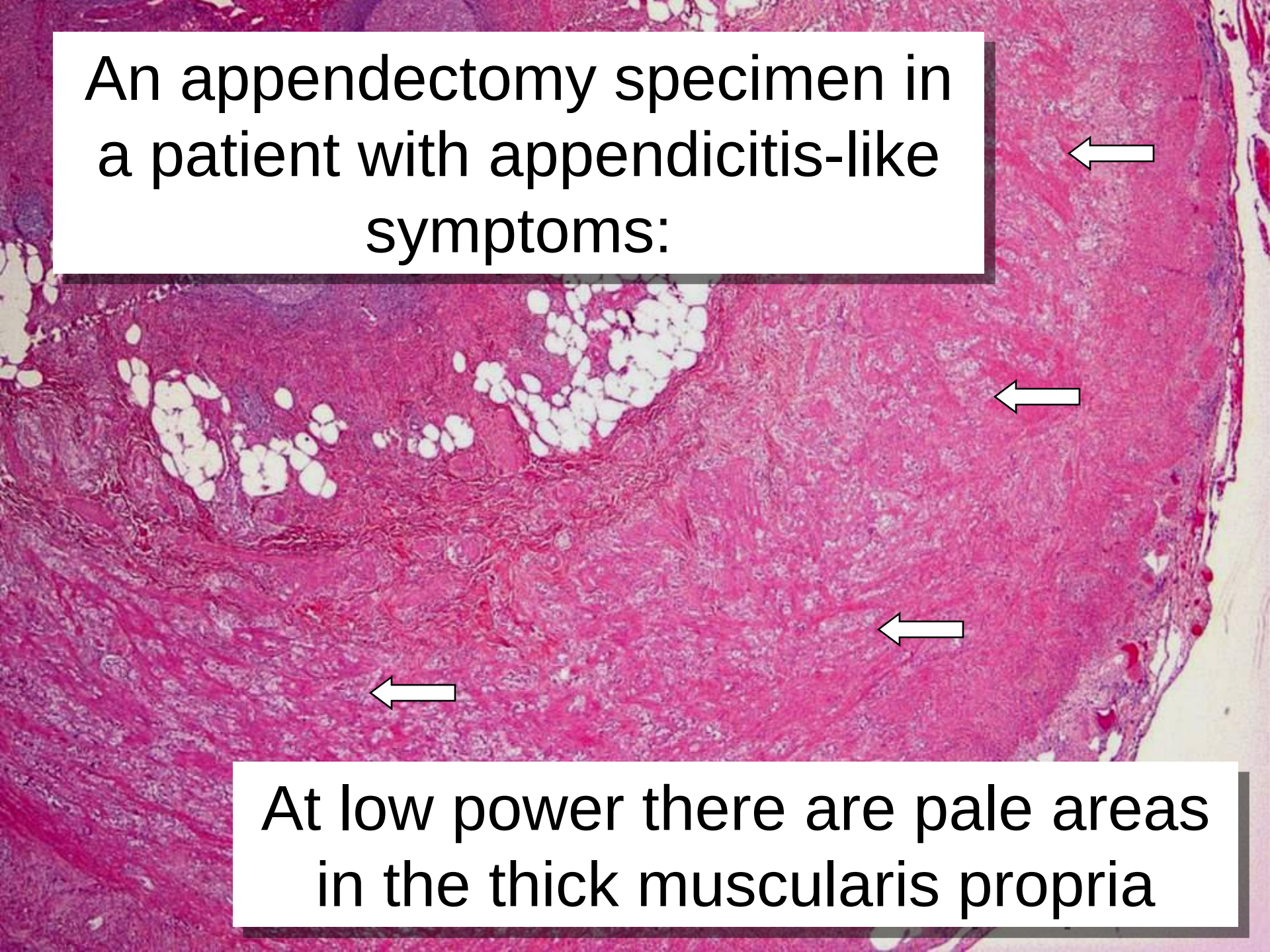
Significance for pathologists

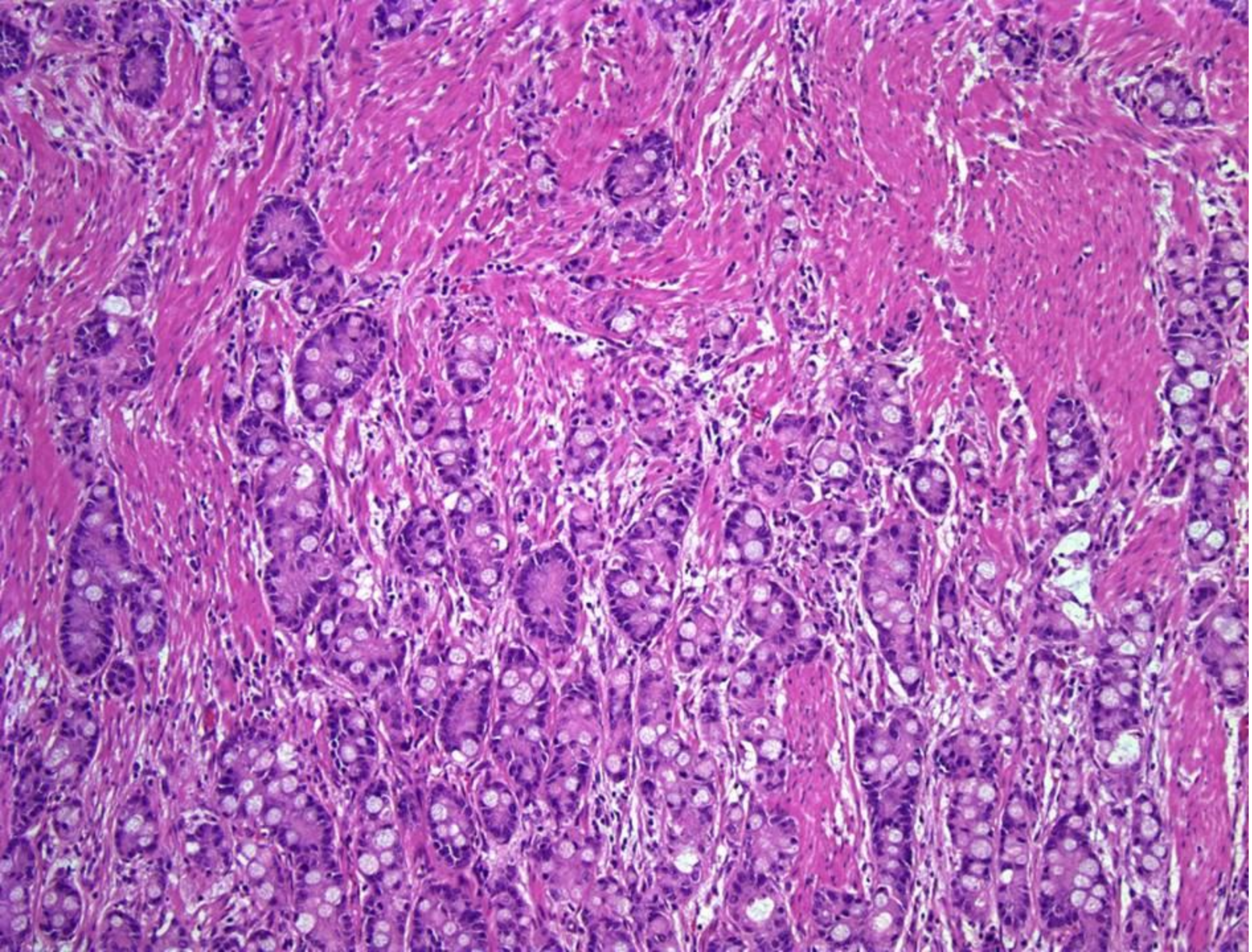
- Frozen sections on appendiceal margins, lymph nodes recommended in surgical literature
- There are also some recommendations for stat cytologic evaluation of peritoneal mucus!
- Grading of epithelium in pseudomyxoma/peritoneal mucinosis is important to management and prognosis!

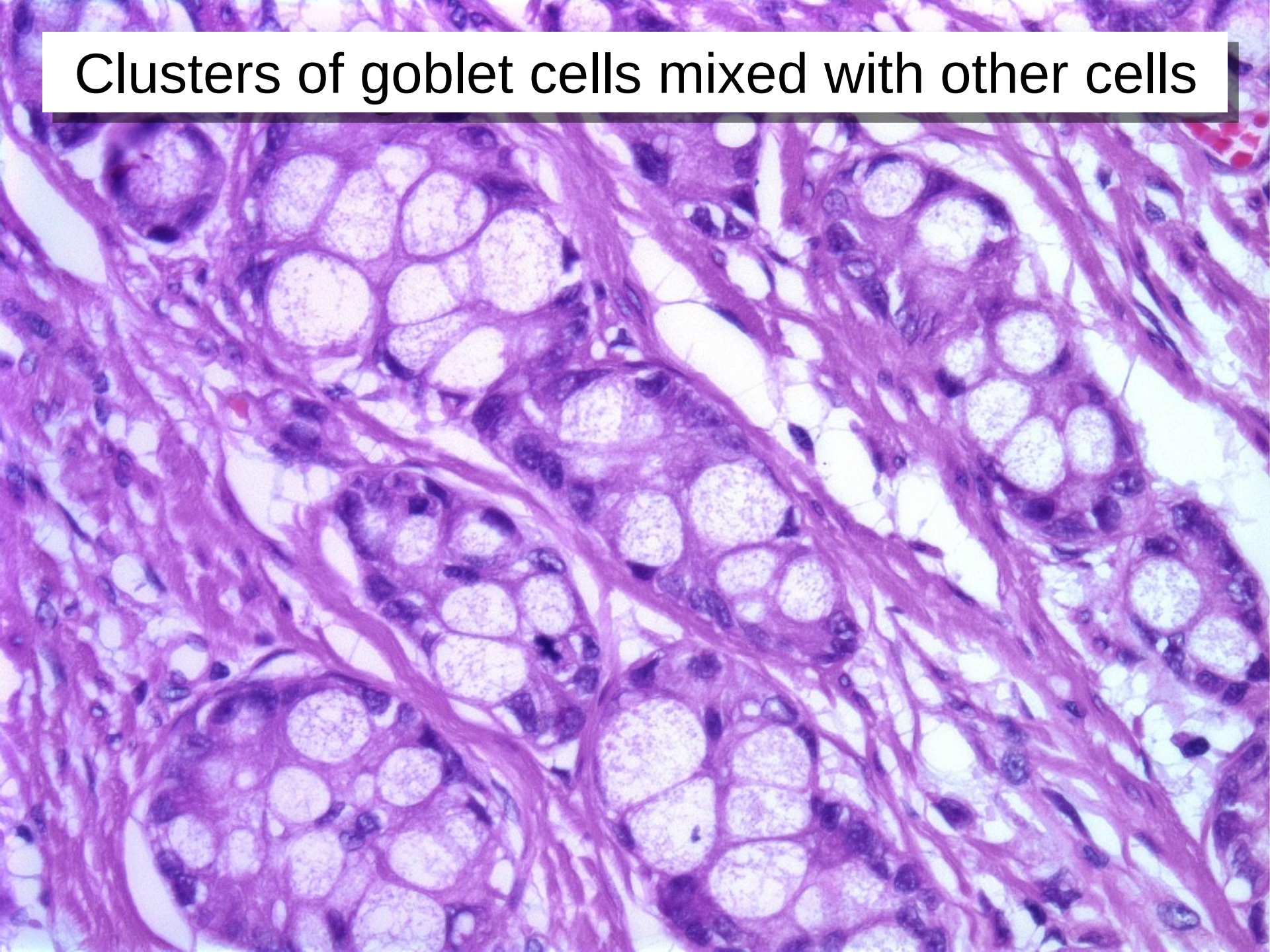
Goblet cell carcinoid tumor of the appendix

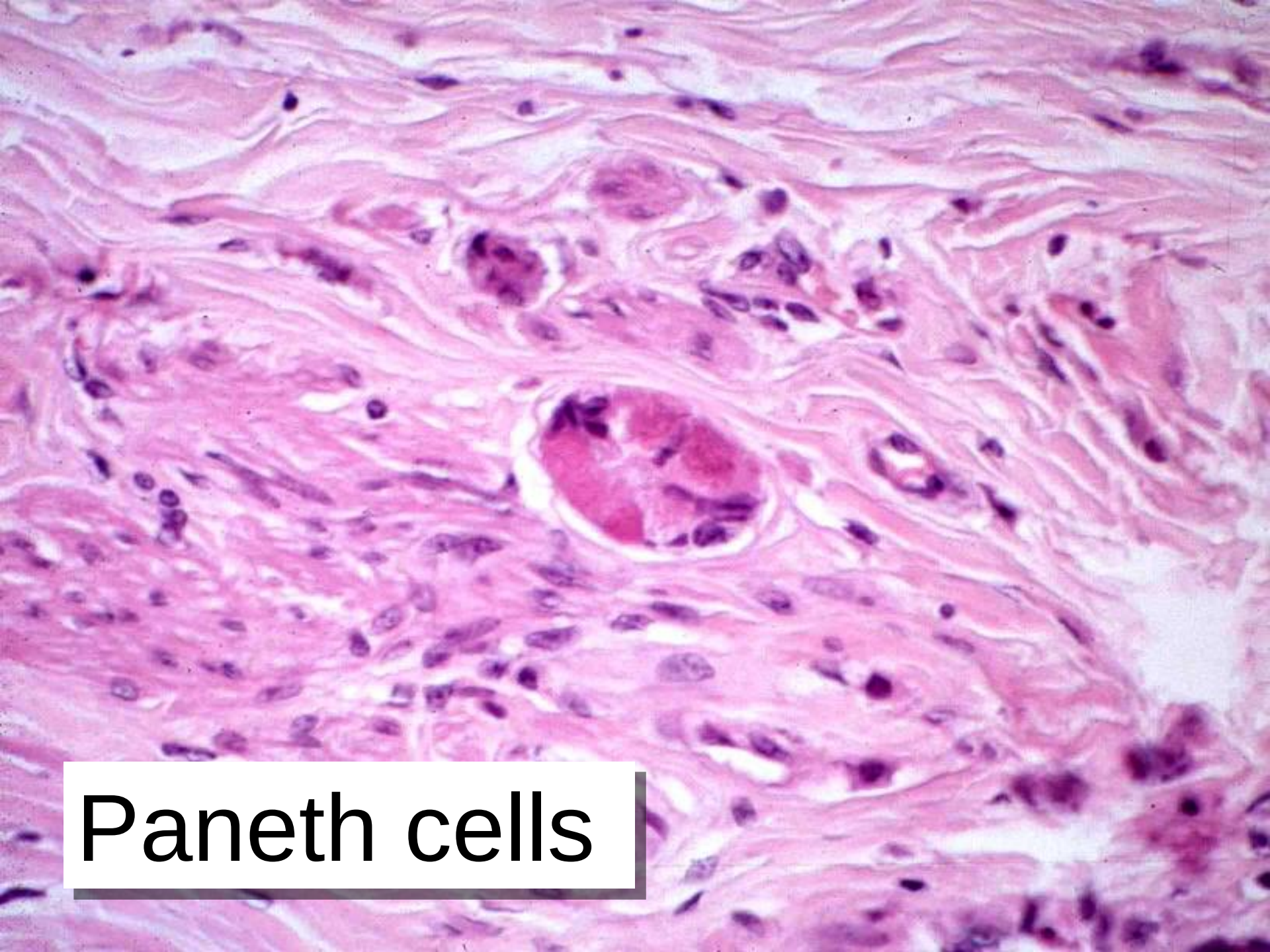
Is this a type of carcinoid tumor, a type of adenocarcinoma, or what?

How does it behave?

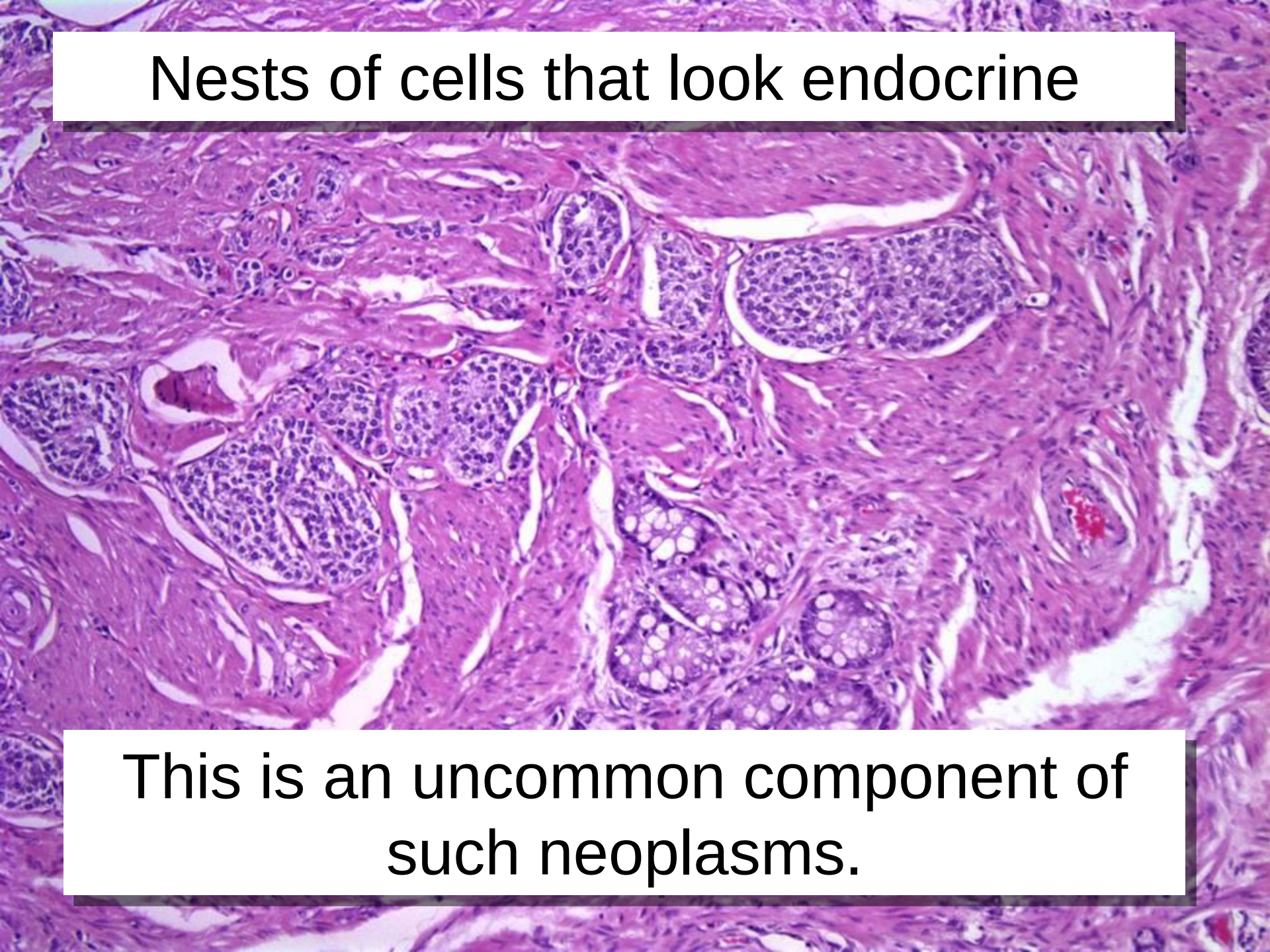

An appendectomy specimen in a patient with appendicitis-like symptoms:
At low power there are pale areas in the thick muscularis propria



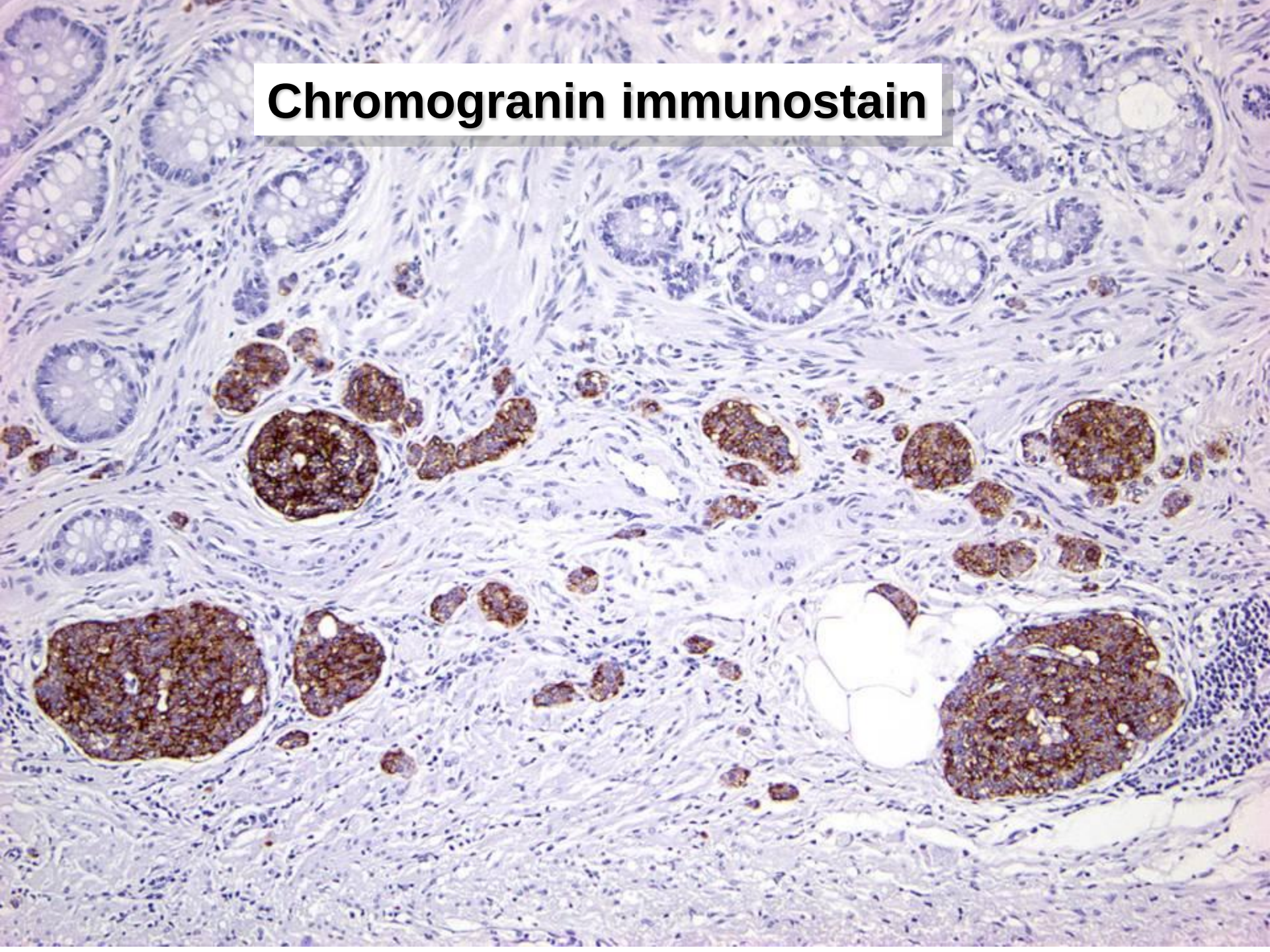

Clusters of goblet cells mixed with other cells


Paneth cells

Nests of cells that look endocrine



This is an uncommon component of such neoplasms.


Chromogranin immunostain

Neurotropism

Many names have been used or proposed for this tumor:

Adenocarcinoma
Goblet cell carcinoid tumor
Mucinous carcinoid
Intermediate type of carcinoid
Crypt cell carcinoma
Microglandular carcinoma
Adenocarcinoid tumor
Carcinoid tumor NOS

The accepted name (WHO) for this is

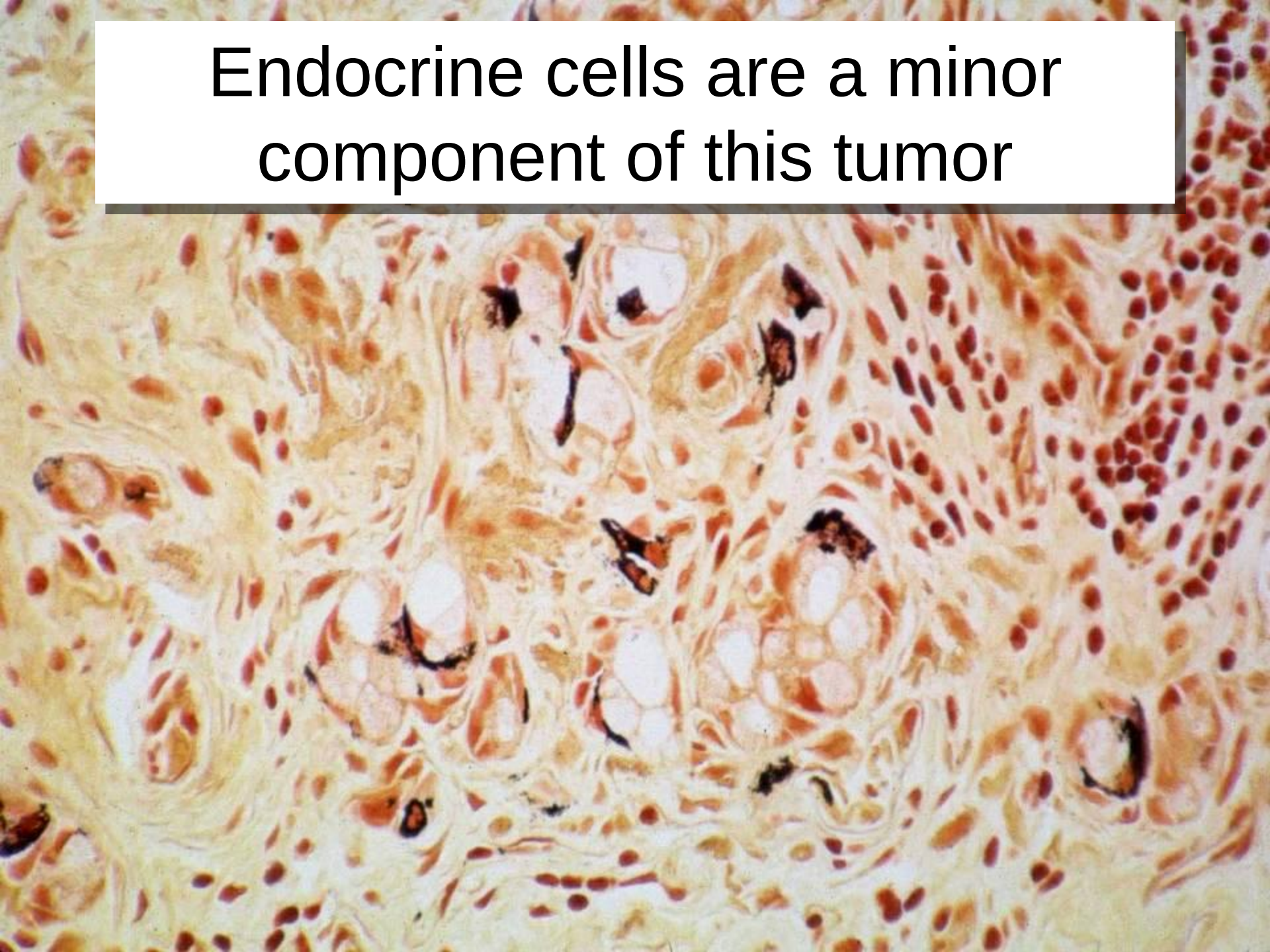
“Goblet cell carcinoid tumor”

Patients generally present with acute appendicitis, and neoplasm is seldom suspected preoperatively.

Some examples are so small and subtle that it is easy to miss them.

Calling this a carcinoid tumor contributes to confusion as to its significance and management.

Endocrine cells are a minor component of this tumor



There are 3 questions that often are asked when these tumors are found:

1. Is this really a type of carcinoid tumor?

2. How will it behave?

3. Should a more extensive resection be done, and under what circumstances?

Ideally, we would answer these questions using solid data.

Most of the literature about this tumor consists of case reports or tiny series, as well as a few review articles by surgeons who did not understand the histologic variations.

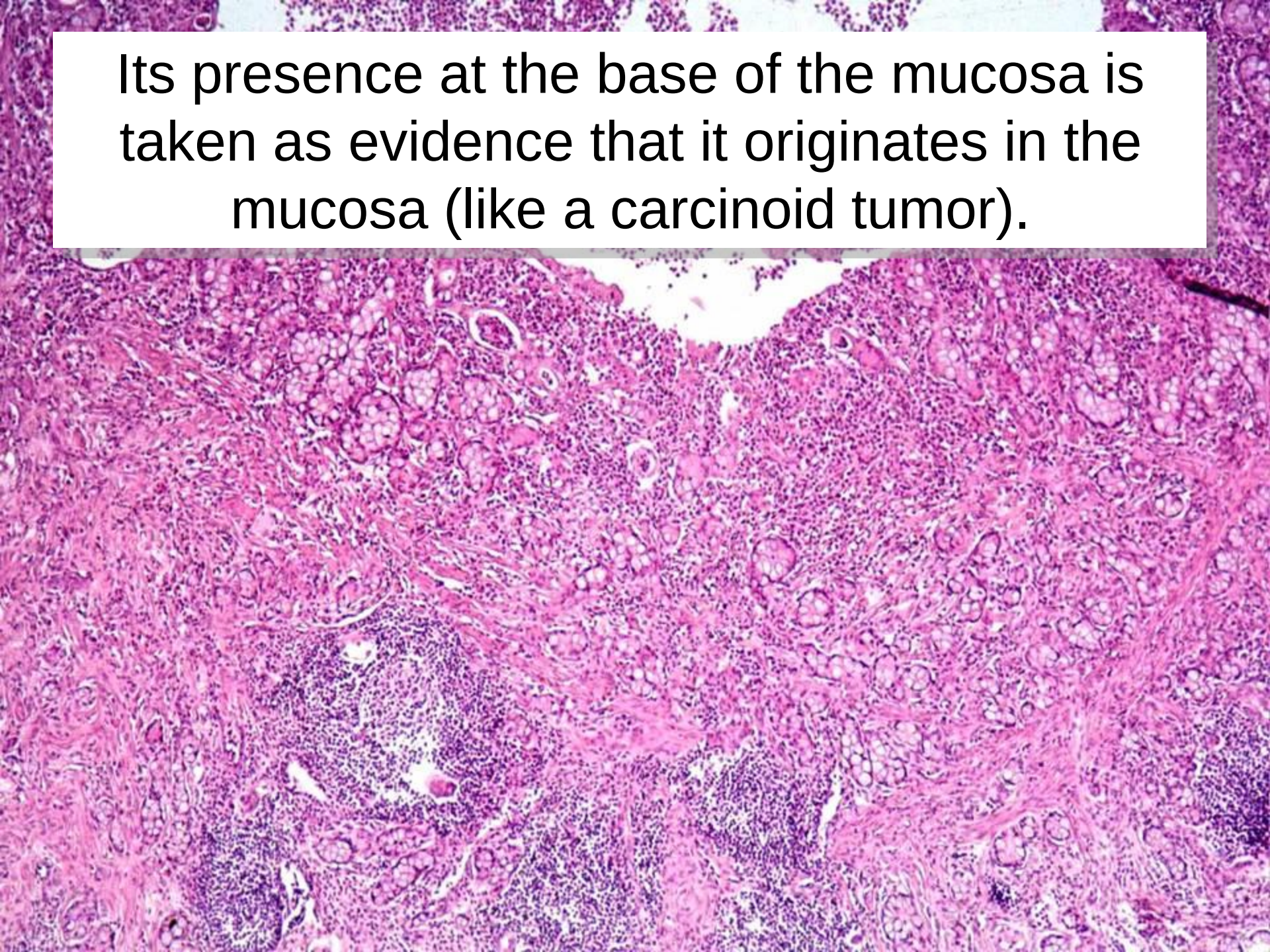
The first question….

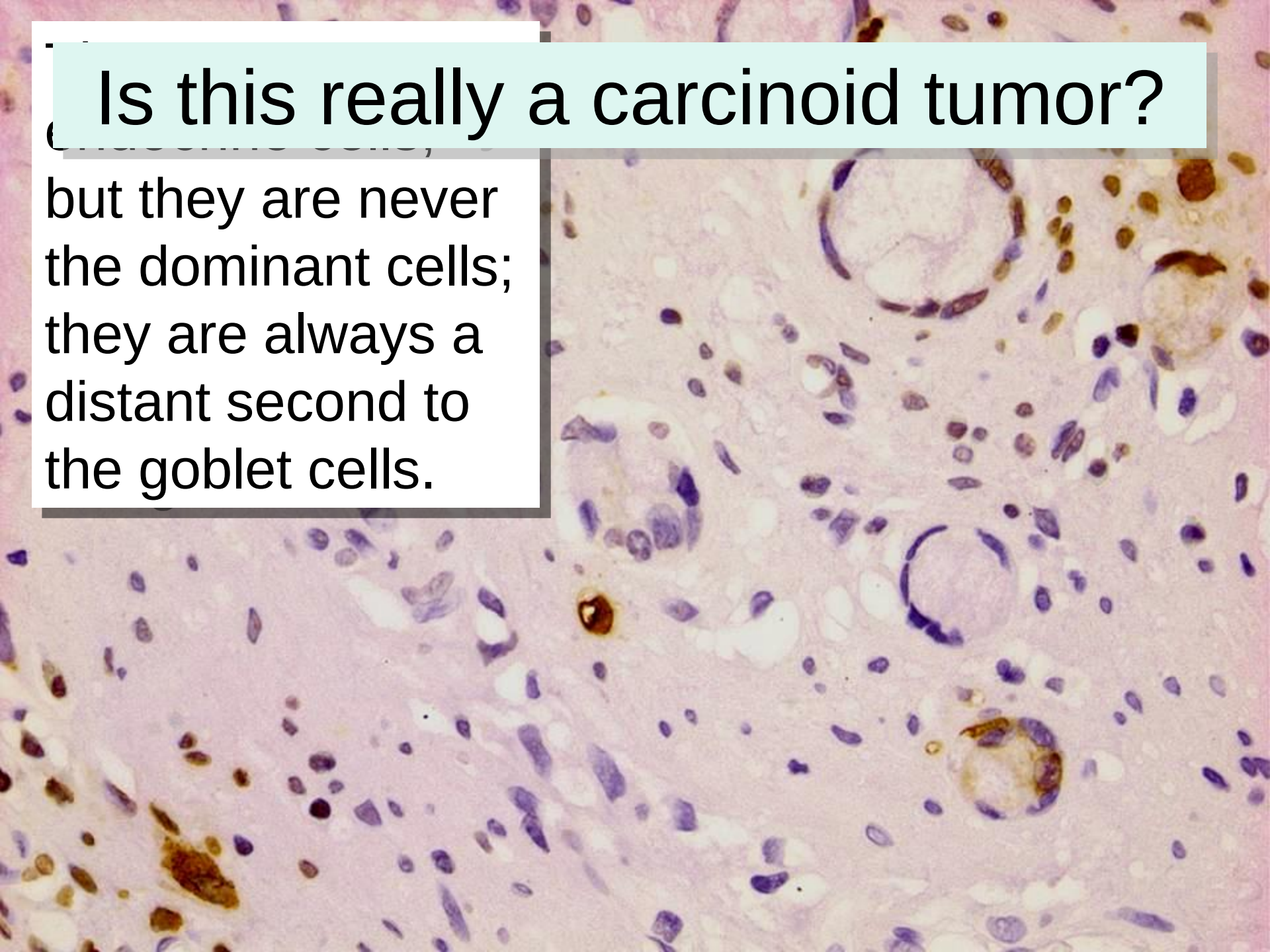
Is this really a carcinoid tumor?

WHO classifies this as an endocrine tumor

Why has it been categorized this way?

Its presence at the base of the mucosa is taken as evidence that it originates in the mucosa (like a carcinoid tumor).





Is this really a carcinoid tumor?

but they are never the dominant cells; they are always a distant second to the goblet cells.

Is this really a carcinoid tumor?

Goblet cell carcinoids share a number of genetic abnormalities with *ileal* carcinoid tumors, including allelic loss of chromosomes 11q, 16q, and 18q, suggesting similar events in the pathogenesis of these tumors.

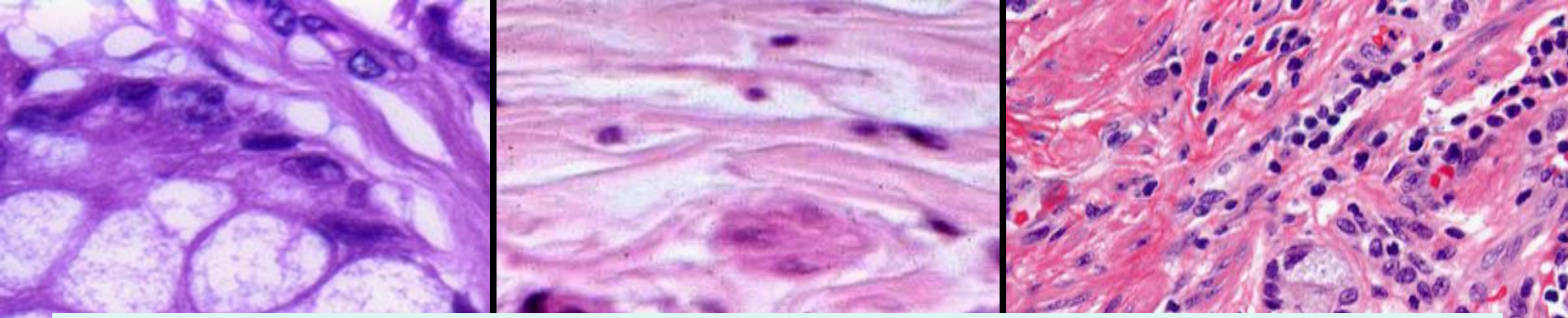
Stancu M, Wu TT, Wallace C, Houlihan PS, Hamilton SR, Rashid A. Genetic alterations in goblet cell carcinoids of the vermiform appendix and comparison with gastrointestinal carcinoid tumors. Mod Pathol. 2003 Dec;16(12):1189-98

In fact, these are heterogeneous tumors

One of the proposed names:

Crypt cell carcinoma

that differentiate along a number of epithelial lines



However, WHO classifies this as an endocrine tumor and calls it goblet cell carcinoid but we stage it like adenocarcinoma

But it has some adenocarcinoma-like features:

Mucin production

Paneth cells

A propensity for spread to ovaries and peritoneal surfaces

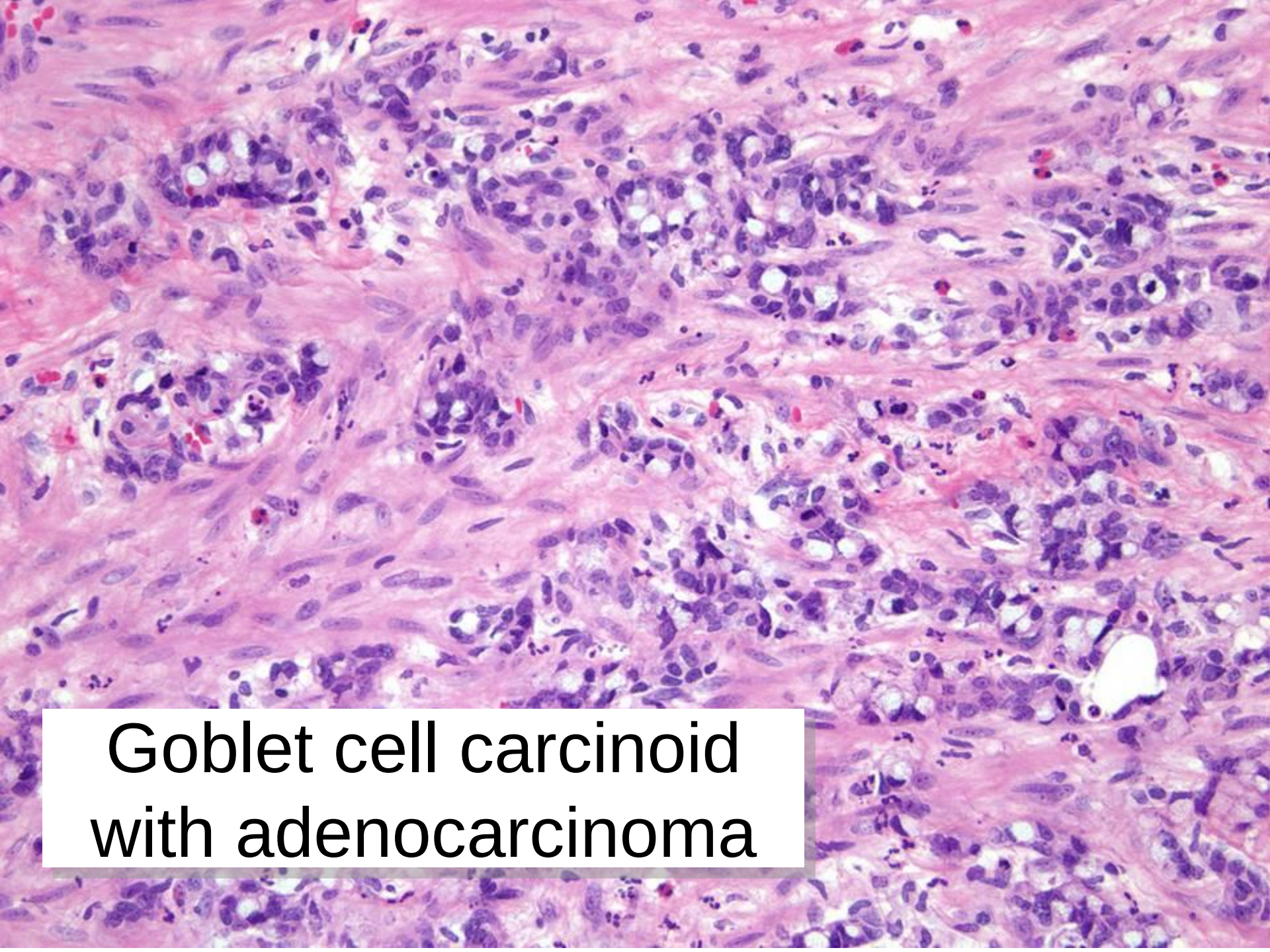
May cause death!

So, if this tumor can be aggressive..

What is known about the long term results following appendectomy?

Two large studies have dealt with this issue:

The authors identify 2 types of goblet cell carcinoid tumors, a pure form and a form that had a mixture of pure areas and carcinoma.


Goblet cell carcinoid
with adenocarcinoma

Goblet cell Carcinoids and Related Tumors

Type	Extent	Mets	Outcome
Pure GCC	**App**	**NO**	**A & W**
Mixed GCC/Adenoca	**App/Invasion**	**Yes**	**80% Fatal AdenoCA**

Burke, et al, Am J Clin Pathol. 94:27-35, 1990

Tang LH, Shia J, Soslow RA, Dhall D, Wong WD, O'Reilly E, Qin J, Paty P, Weiser MR, Guillem J, Temple L, Sobin LH, Klimstra DS. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. Am J Surg Pathol. 2008 Oct;32(10):1429-43.

Goblet Cell Carcinoid	• Well differentiated goblet cells arranged in clusters or in a linear pattern • Minimal cytologic atypia • Minimal desmoplasia • Degenerative change with extracellular mucin is acceptable
Adenocarcinoma Ex GCC, Moderately Differentiated	• Recognizable GCC tumor cells arranged or fused into irregular clusters; • Recognizable GCC tumor cells with easily identifiable single file or single cell infiltration • Significant cytologic atypia • Marked desmoplasia
Adenocarcinoma Ex GCC, Poorly Differentiated	• Requires at least focal evidence of goblet cell morphology • A component (> 1 high power field or >0.5 mm^2) is not otherwise distinguishable from a poorly adenocarcinoma ➢ confluent sheets of signet ring cells or undifferentiated cells ➢ malignant cribriform glands or glandular epithelium

Study of 63 cases of appendiceal goblet cell carcinoid tumor by Tang, et al, from MSK and AFIP

	N	Mean F/U (mo)	Mean survival (mo)	NED	AWD	DOD
All	**61**	**49**	**43**	**28 (46%)**	**19 (31%)**	**14 (23%)**
GCC	**28**	**66**	**119**	**24 (86%)**	**3 (11%)**	**1 (4%)**
WD Ca ex GCC	**26**	**35**	**43**	**4 (15%)**	**15 (58%)**	**7 (27%)**
PD Ca ex GCC	**7**	**29**	**31**	**0 (0%)**	**1 (14%)**	**6 (86%)**

Stage matters,too:

Mayo Clinic study of 57 patients with goblet cell carcinoid

5 year survival (%)	
Stage I	100
Stage II	76
Stage III	22
Stage IV	14

Recurrence rate (%)	
T 1 or 2	0
T 3	33
T 4	71

Pham, et al. Surgical and chemotherapy treatment outcomes of goblet cell carcinoid: a tertiary cancer center experience. Ann Surg Oncol 2006;13:370-6

Pure low grade GCC confined to the appendix do very well.

GCC that have a component of frank adenocarcinoma, and those that are advanced at presentation do worse.

The third question…

Should a more extensive resection be done, and, if so, under what circumstances?

This is a great question and one that commonly accompanies our consults on this tumor.

Unfortunately, there are no hard data and no controlled studies.

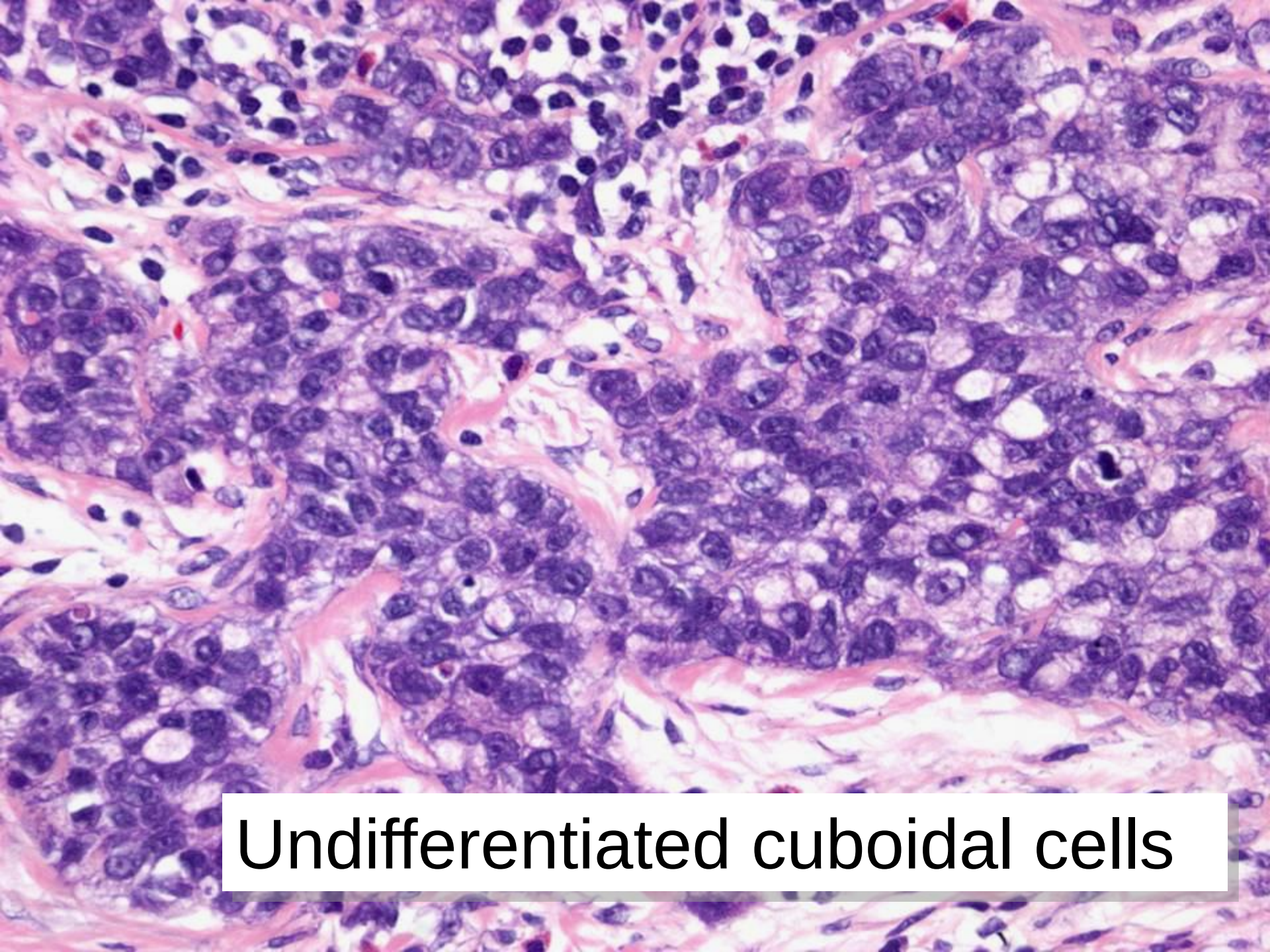
The primary treatment is surgical.

Which patients need a hemicolectomy is the issue, and there are no universally accepted guidelines.

Which patients require a hemicolectomy?

In general, there seems to be consensus on the following:

- Extension outside appendix (no clear appendiceal margin, peritoneal or ovarian involvement, lymph node mets)
- Clear adenocarcinomatous component


Undifferentiated cuboidal cells

What do we need to tell the surgeon about a goblet cell carcinoid (GCC)?

Pure GCC or adenocarcinoma

TNM

Appendiceal margin

Other staging information, if we have the tissue: lymph nodes, ovaries, peritoneal spread


E
600 EASY ST