GIS

Sheet no. 8

Pathology

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Colonic Adenocarcinoma

- **Most common malignancy of the gastrointestinal tract.**
- Small intestine is uncommonly involved by neoplasia as most intestinal tumors are in the colon.
- Peak: 60 to 70 years. 20% under 50 years. It's a disease of elderly (risk increases with age, except for familial tumors).
- Developed countries lifestyles and diet that includes **low intake of vegetable fiber and high intake of carbohydrates and fat**. Ongoing evidence shows that red meat is associated with increased risk of colonic adenocarcinoma, while fibers are protective. Diet is a very important risk factor that carries carcinogens which are considered the driving force for developing adenocarcinoma.
- Aspirin or other NSAIDs have a **protective** effect. As cyclooxygenase-2 promotes epithelial proliferation and these drugs inhibit COX-2 suppressing epithelial proliferation.

Pathogenesis

Heterogeneous molecular events. The pathogenesis is multifactorial and multiple genes are involved. During its development, accumulation and acquisition of multiple different mutations takes place.

Sporadic cases are more common than familial ones just like other types of malignancies.

- **Two pathways involved in both familial and sporadic cases:**

1. APC/β-catenin pathway >> increased WNT signaling. (Recall that APC gene mutation is involved in the pathogenesis of FAP as well).
2. Microsatellite instability pathway due to defects in DNA mismatch repair. (Recall that it's also involved in HNPCC)

Stepwise accumulation of multiple mutations.

The APC/β-catenin (chromosomal instability) pathway:

It's the classic pathway in adenoma carcinoma sequence (most common pathway). Adenomas which are precursors of carcinomas take this pathway in their transformation in 80% of sporadic colon tumors.

APC is a key negative regulator of β-catenin, a component of the WNT signaling pathway.

Mutation of the **APC tumor suppressor gene** is the **EARLY EVENT** as it's the earliest change that occurs in the adenoma to carcinoma sequence:

Loss of APC and its negative control of β-catenin → accumulation of β-catenin → enters nucleus → MYC and cyclin-D1 transcription → promote proliferation and further accumulation of subsequent mutations.

Both copies of APC should be inactivated for adenoma to develop. 1st allele mutation is considered the 1st hit and the 2ndallele mutation is the 2nd hit and they're both required to initiate the process.

Acquisition of additional mutations is the **LATE EVENT** seen in larger adenomas and invasive tumors rather than early smaller adenomas, examples include:

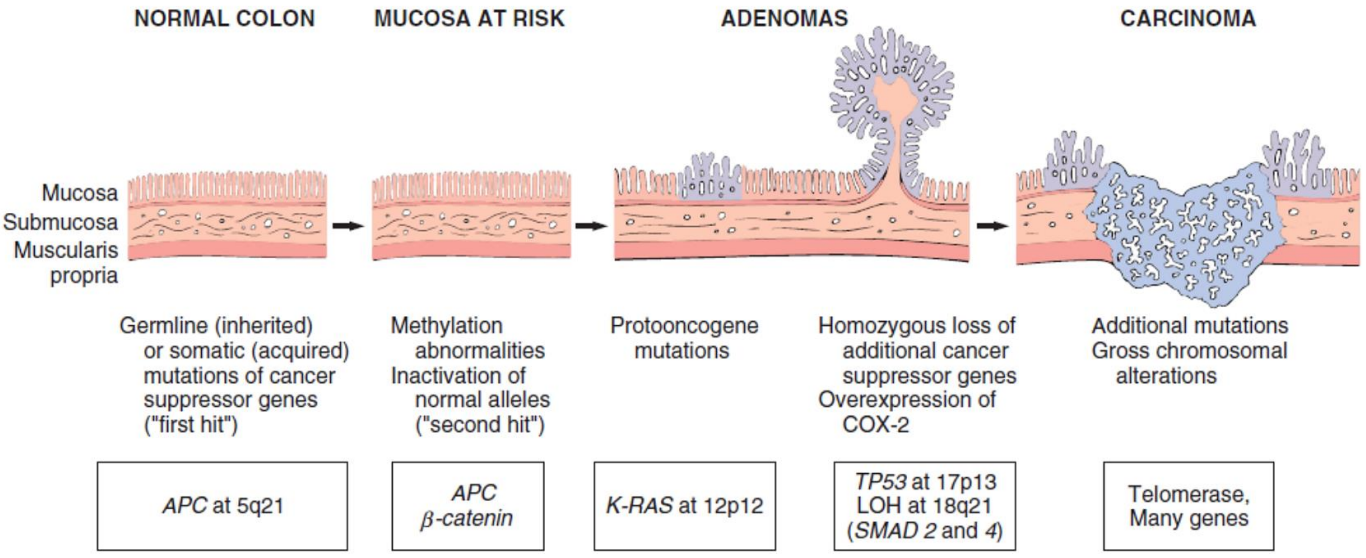
KRAS oncogene mutation and activation.

SMAD2 and **SMAD4 tumor suppressor genes** mutations and inactivation.

TP53 tumor suppressor gene is mutated (inactivation mutation) in 70% -80% of colon cancers which is also a late event in adenomas and INVASIVE cancer so it may not be seen in an early small colonic adenoma.

Later, the expression of telomerase also increases as the tumor advances.

this figure summarizes the pathway:



Normal colon becomes at risk as mutations start to appear then adenoma development and enlargement takes place and finally it turns into an invasive carcinoma.

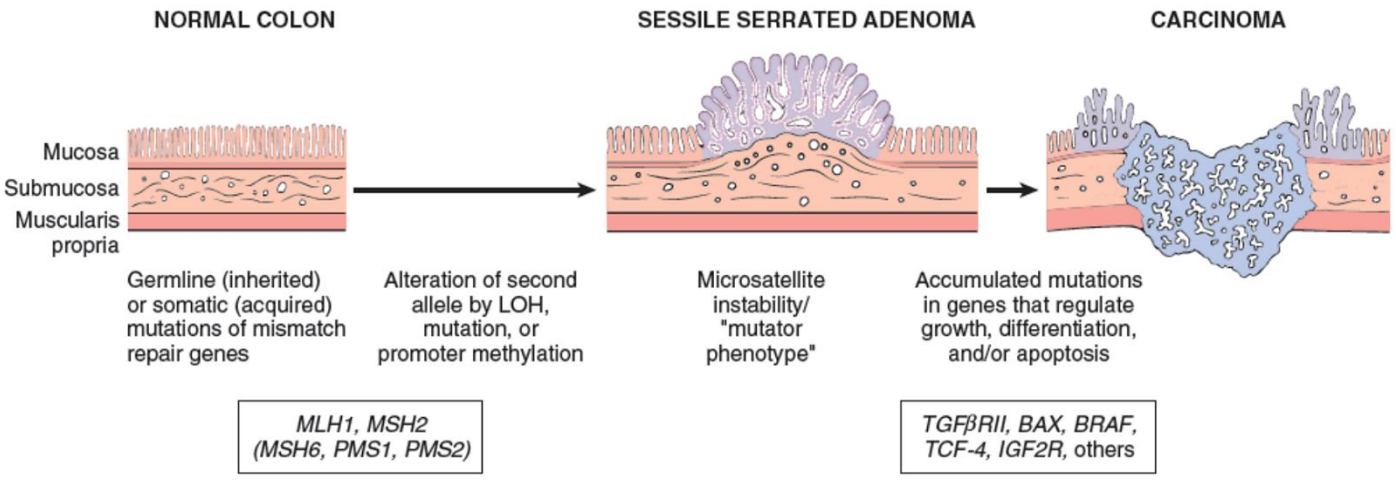
starting with APC mutation. First hit can be germline (familial) or acquired. If inherited, it takes a short time for the second hit to occur. Therefore, cancer appears at an earlier age in familial cases. However, both hits are acquired in sporadic cases causing the cancer to appear at an older age. After both hits occur, β-catenin accumulates. Notice how at this stage there is still no adenoma nor dysplasia indicating how early these changes are that they take place even before the formation of a colonoscopically detectable mass or lesion. Then, later events take place; K-RAS mutation and others. The tumor starts to enlarge increasing the risk of progression. Further mutations accumulate and an invasive grossly visible cancer with marked chromosomal alterations and increased expression of telomerase appears.

The microsatellite instability pathway:

DNA mismatch repair genes mutation and deficiency.

Loss of mismatch repair genes→ introduction of errors in DNA replication→ Mutations accumulate in microsatellite repeats (very short repeats) → Microsatellite instability.

These mutations are silent if microsatellites are located in noncoding regions. But, if located in coding or promoter regions of genes involved in cell growth and apoptosis (TGF-B and BAX genes) they result in uncontrolled growth, inhibition of apoptosis and tumor development.



Starts with a mutation in a DNA mismatch repair gene (MH1,MSH2,..) that can be inherited or acquired and the second copy of the gene should be inactivated as well leading to microsatellite instability and formation of a peculiar adenoma of a special type (sessile serrated adenoma; no stalk) that is different from adenomas of the first pathway but a also carries the risk of transformation by acquisition of more mutations in different genes like apoptotic genes and genes responsible for cellular proliferation leading to more proliferation, growth and inhibition of apoptosis and development of invasive adenocarcinoma.

Important!!

Right sided tumors are highly associated with microsatellite instability

Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	*APC*	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%)	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%–15%)	DNA mismatch repair	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

Morphology

Macroscopic: (seen during colonoscopy)

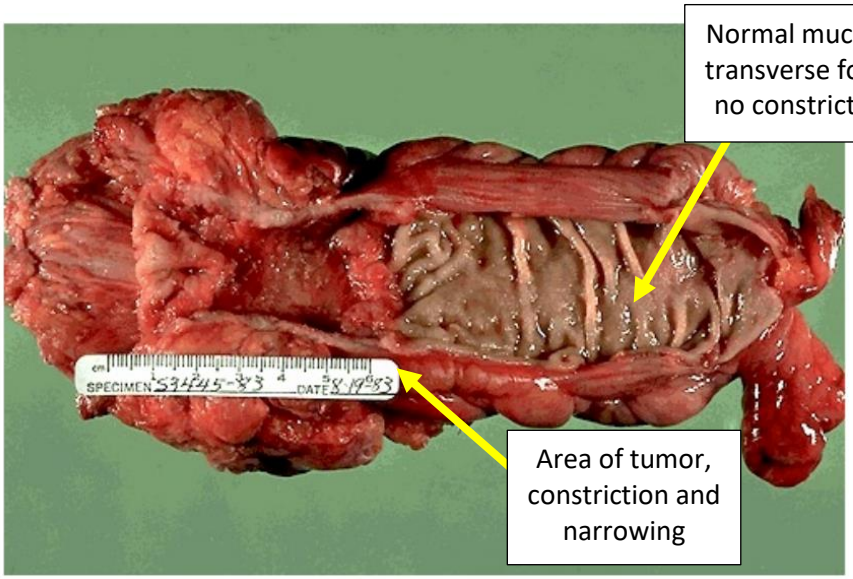
Proximal colon tumors: polypoid, exophytic masses that protrude into the lumen but rarely cause obstruction because of the wide lumen of the cecum. Usually right sided/ proximal adenocarcinomas present late because the tumor causes no symptoms even if large.

Distal colon: can form masses (polypoid, exophytic) as well as annular lesions "**napkin ring**" (constrictions & narrowing), presenting with intestinal obstruction leading to earlier detection.

Microscopic:

- **Dysplastic GLANDS** with **strong desmoplastic response** (reaction of collagen deposition, edema and fibroblastic proliferation around the tumor. -***indicator of invasion***).
- An important feature of **colonic** cancer is **dirty necrosis**. Necrotic debris are typical.
- Some tumors give abundant mucin or form signet ring cells.

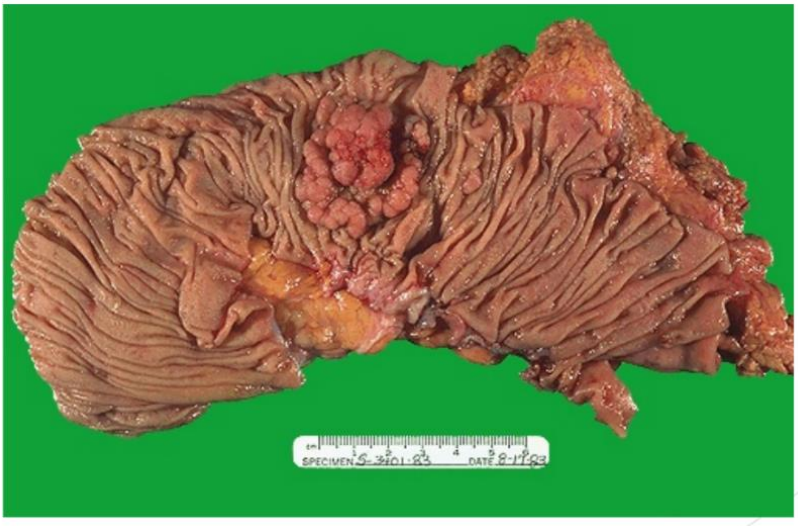
Rectosigmoid adenocarcinoma (LEFT SIDED/DISTAL), napkin ring



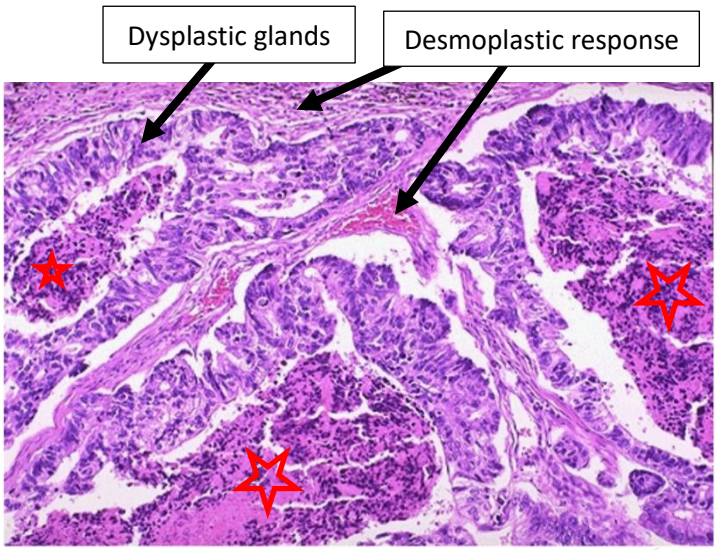
Napkin ring

Exophytic adenocarcinoma

Forms a mass like most tumors, causes obstruction if **left** sided.

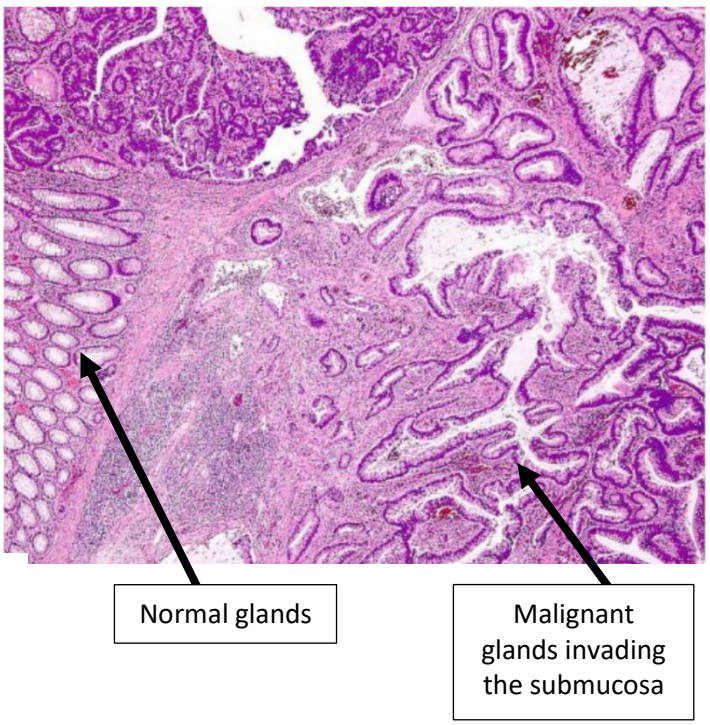


Adenocarcinoma with necrosis



★ dirty necrosis (indicates invasion)
note: dysplastic glands are also seen in adenomas but when accompanied with dirty necrosis and desmoplastic response (clues of **invasion**) they indicate invasive adenocarcinoma.

Invasive carcinoma



Clinical Features

Endoscopic screening is important in cancer prevention and early detection as most colon cancers are detected in a late advanced stage. screening is offered in western countries for everyone above **50** and for those with **family history** of colon cancer at an early age.

Early cancer is **asymptomatic**!!!!!!!! Which makes screening very important.

Cecal and right sided cancers: often diagnosed late. Only feature is fatigue and weakness (iron deficiency anemia). As exophytic tumors can cause abrasions, ulcerations and bleeding.

Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise.

Left sided carcinomas: occult bleeding (مخفي detected in the lab by stool for occult blood test), changes in bowel habits is an important symptom, cramping, left lower-quadrant discomfort.

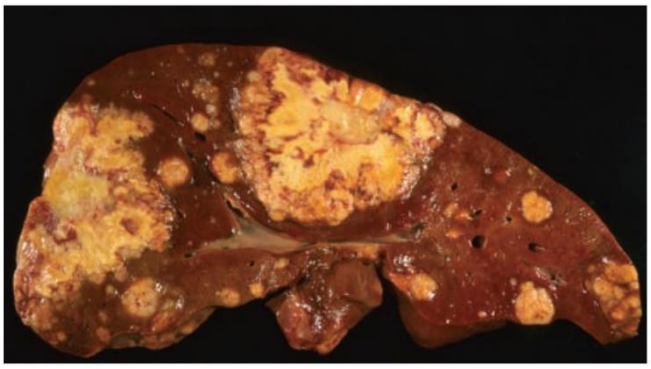
Clinical features may not be specific. However, there are certain alarming features that you must take into consideration and further investigate.

Most important two prognostic factors are: Depth of invasion (T stage) & Lymph node metastasis(N stage).

Other factors that are not as important: Poor differentiation and mucinous histology→ poor prognosis.

Distant metastases (M stage) (lung and liver most commonly) **can be resected.**

Liver metastasis



Appendix

- Normal true diverticulum of the cecum.

Acute appendicitis

Is a surgical emergency that is most common in adolescents and young adults but may occur in any age.

Symptoms can be similar to other diseases making it difficult to confirm preoperatively. Doctors must have a high index of suspicion because it's better to operate and remove a normal appendix than risking its perforation and resultant peritonitis.

Differential Diagnosis DDx:

- **Mesenteric lymphadenitis (inflammation of mesenteric lymph nodes following a viral infection).**
- **Acute salpingitis (inflammation of fallopian tubes), Ectopic pregnancy (pregnancy outside the uterus), Mittelschmerz (midcycle pain/ pain associated with ovulation), Ovarian cysts torsion or rupture. So female patients may be referred to a gynecologist to rule out such conditions.**
- **Meckel diverticulitis.**
- **Crohn disease with terminal ileitis.**

Underlying cause:

Obstruction by fecalith, less commonly: gallstone, tumor, worms….

Luminal obstruction in 50-80% of cases →increased luminal pressure → impaired venous drainage → congestion, ischemic injury & stasis associated bacterial proliferation → inflammatory response rich in neutrophils & edema.

Acute appendicitis isn't considered a bacterial infection. Bacterial overgrowth is a consequence of obstruction.

Older patient in their 60s with appendicitis is questionable and could indicate that they have cancer in their cecum obstructing their appendix.

Diagnosis:

Golden standard for histopathologic diagnosis is the presence of a *neutrophilic infiltration of the muscularis propria.* if not present then it's not considered an acute appendicitis.

Acute suppurative appendicitis is more severe with extensive neutrophilic infiltration that can lead to focal abscess formation.

Acute gangrenous appendicitis: necrosis and ulceration.

Perforation can occur if the patient is not diagnosed early and the inflammation continues resulting in peritonitis.

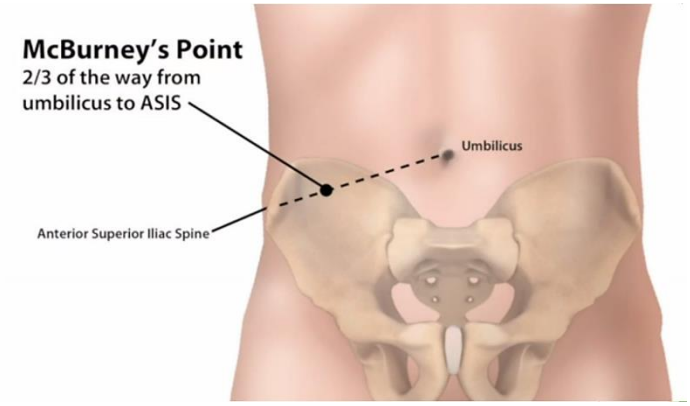
Clinical Features

Early acute appendicitis: periumbilical pain (referred pain)

Later: pain localizes to the right lower quadrant

nausea, vomiting, low-grade fever, mildly leukocytosis (not all symptoms are necessarily present)

A classic physical finding is McBurney's sign (McBurney's point): the physician applies pressure with their fingers then relieves it causing the patient to complain of severe pain upon the relief. This sign can be absent early on.



Signs and symptoms are often absent especially early on, creating difficulty in clinical diagnosis.

Tumors of the appendix (rare)

The most common tumor: carcinoid (neuroendocrine tumor)

Incidentally found during surgery or on examination of a resected appendix.

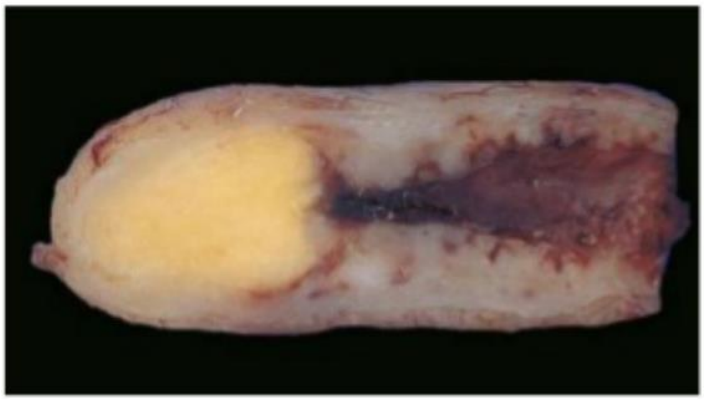
Distal tip of the appendix is the most common location.

Nodal metastases & distant spread are rare as they usually behave in a benign fashion and have good prognosis. Thus, the association with carcinoid syndrome is not common as it requires a metastatic tumor to occur.

Carcinoid tumor

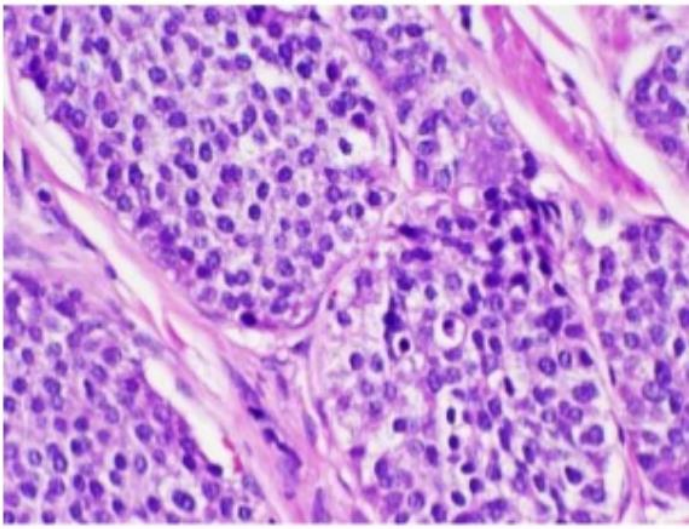
Gross

Well circumscribed, yellow, at the tip of the appendix



Microscopic

Similar to neuroendocrine tumors in other locations in the body. Nesting pattern, salt and pepper appearance of nuclei, abundant cytoplasm.



GOOD LUCK