MCB 458 Case 1
16-year-old with Jaundice

Cody Lund
Judy Nguyen
Mariam Arif
Marc Sleiman
4 Days Prior: 
Home
- Pruritus at ankles
- Malaise
- Stomach cramping

3 Days Prior: 
Home
- Diffuse pruritus
- Fatigue
- Reduced appetite

2 Days Prior: 
Home
- Food tastes “funny”
- Malaise
- Fatigue
- Dark Urine
- Pale

1 Day Prior: 
School/First Hospital
- Malaise
- Jaundice
- Conjunctival Icterus

Admission: 
Second Hospital
- Malaise
- Abdominal pain
- Jaundice
- Conjunctival Icterus
1 Day Prior to Admission (referred to emergency department of another hospital)

Vitals:

- Temp: 36.7°C (98.06°F)
- Pulse of 100 bpm
- Blood pressure of 139/82 mm Hg
- Respiratory rate 20 breaths per min
- Oxygen saturation 98%

No abdominal tenderness. Rest of physical examination was normal
The patient presented with jaundice, a condition which causes the skin and whites of eyes to turn yellow. What is likely elevated in this patient?

A. Glucose  
B. Iron  
C. Calcium  
D. Bilirubin  
E. Glutamate
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B. Iron
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Patient Presentation and Initial Chief Complaint at Second Hospital

- Generally healthy 16-year-old boy
- Presented with malaise, fatigue, and jaundice
- Abdominal pain rating is 6 on a scale of 0 to 10, with 10 indicating the most severe pain
What is your hypothesized diagnosis from the initial patient presentation?

A. Hepatitis
B. Cancer
C. Liver Disease
D. Cirrhosis
E. Gilbert's syndrome
During Admission to Second Hospital

- The patient reported mild, diffuse pruritus, which was most prominent on the upper back, and mild, diffuse abdominal pain.
- No change in rest of physical exam.
- The patient received treatment with oral ursodiol and vitamin E and intramuscular vitamin K.
Ursodiol is a naturally occurring bile acid. What properties of vitamin E and vitamin K would explain why the physician administered them to the patient with bile acid?

A. Vitamins E and K are water soluble
B. Vitamins E and K are fat soluble
C. Vitamin E is water soluble, vitamin K is fat soluble
D. Vitamin K is water soluble, vitamin E is fat soluble
E. None of the above
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C. Vitamin E is water soluble, vitamin K is fat soluble
D. Vitamin K is water soluble, vitamin E is fat soluble
E. None of the above
Patient Background
Initial Vitals

Patient Vitals

Temperature: 36.8°C
Pulse: 80 beats per minute
Blood pressure: 134/59 mmHg
Respiratory rate: 20 breaths/min
Oxygen saturation: 99% in ambient air

Reference Vitals

Temperature: 36.1°C to 37.2°C
Pulse: 70 – 100 beats per minute
Blood pressure: ???? mmHg
Respiratory rate: 12 – 20 breaths/min
Oxygen saturation: 95% – 100% in ambient air
What is the range for normal blood pressure (in mmHg)?

A. Less than 120 and 80
B. Between 120–129 and less than 80
C. Between 130–139 or 80–89
D. Greater than or equal to 140 or 90
E. Greater than or equal to 180 and/or 120
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A. Less than 120 and 80
B. Between 120-129 and less than 80
C. Between 130-139 or 80-89
D. Greater than or equal to 140 or 90
E. Greater than or equal to 180 and/or 120
Patient Background

- Lives with parents and two dogs in a heavily forested, rural area of New England
- Has not traveled recently
- No known exposure to sick persons
- Five days prior to the onset of illness, he ate fast food
- Not sexually active
- Does not smoke cigarettes, drink alcohol, or use illicit drugs
Patient Medical History

- Had a tonsillectomy in the past
- Never received a blood transfusion
- Does not take any medication or herbal or dietary supplements
- No known allergies
- Immunizations are up to date
Family History

- Patient’s mother became jaundiced and had abnormally elevated results of liver-function tests
  - No specific diagnosis and illness resolved by itself
- Patient’s maternal grandfather had non-alcoholic fatty liver disease and brain cancer
- Patient’s maternal second cousin had systemic lupus erythematosus
  - Causes inflammation in affected tissues
  - Symptoms: fatigue, malaise, fever, loss of appetite, weight loss, joint pain and rash
Key Points in Patient History, Family History, and Vitals

- Lives in a wooded area of New England
- Does not smoke, drink, or use illicit drugs
- Family history of liver disease
- High blood pressure
Lab Tests and Results
Lab tests

- Complete blood cell count
  - Evaluate overall health
- Red-cell indices were normal in previous and current hospital tests
<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Range, Other Hospital</th>
<th>On Presentation, Other Hospital</th>
<th>Reference Range, This Hospital</th>
<th>On Presentation, This Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.0–16.0</td>
<td>12.2</td>
<td>13.0–16.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>36–49</td>
<td>36</td>
<td>37.0–49.0</td>
<td>33.2</td>
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<tr>
<td>White-cell count (per μl)</td>
<td>4500–13,000</td>
<td>700</td>
<td>4500–13,000</td>
<td>900</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td>64</td>
<td></td>
<td></td>
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<tr>
<td>Monocytes</td>
<td></td>
<td>8</td>
<td></td>
<td></td>
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<tr>
<td>Atypical lymphocytes</td>
<td></td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (per μl)</td>
<td>150,000–400,000</td>
<td>95,000</td>
<td>150,000–450,000</td>
<td>92,000</td>
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<td>Red-cell count (per μl)</td>
<td>4,100,000–5,100,000</td>
<td>4,090,000</td>
<td>4,500,000–5,300,000</td>
<td>4,030,000</td>
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<td>11.0–14.0</td>
<td>16.1</td>
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<tr>
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<td></td>
<td>0.9–1.1</td>
<td></td>
<td>1.3</td>
</tr>
</tbody>
</table>
Lab tests

- **Basic Metabolic Panel**
  - blood levels of electrolytes, glucose, amylase, lipase and acetaminophen were normal
  - The results of renal-function tests were normal

- **Urinalysis**
  - Urinalysis showed clear, amber urine with moderate bilirubin and trace albumin

- **Bilirubin blood test**

<table>
<thead>
<tr>
<th>Bilirubin (mg/dl)</th>
<th>Total</th>
<th>Direct</th>
<th>Ceruloplasmin (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.2–1.2</td>
<td>8.5</td>
<td>0–1.0</td>
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<tr>
<td></td>
<td>0.0–0.5</td>
<td>6.3</td>
<td>0–0.4</td>
</tr>
</tbody>
</table>

- **Test for Wilson’s Disease**
Lab tests

- Tests for infections
  - HIV
  - Hepatitis A, B and C
  - EBV
  - Cytomegalovirus
  - Borrelia burgdorferi
  - antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies, and anti-liver-kidney microsomal type 1 antibodies were all negative

- All serological tests were negative
Lab tests

- **Test for protein levels**

<table>
<thead>
<tr>
<th>Protein (mg/dl)</th>
<th>6.1–8.2</th>
<th>6.1</th>
<th>6.0–8.3</th>
<th>5.8</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.4–5.0</td>
<td>3.8</td>
<td>3.3–5.0</td>
<td>4.1</td>
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<tr>
<td>Globulin</td>
<td>2.5–4.3</td>
<td>2.3</td>
<td>1.9–4.1</td>
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</table>

- **Test for aminotransferases**

<table>
<thead>
<tr>
<th>Aminotransferase (U/liter)</th>
<th>0–55</th>
<th>3058</th>
<th>10–55</th>
<th>2839</th>
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</thead>
<tbody>
<tr>
<td>Alanine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate</td>
<td>15–37</td>
<td>1664</td>
<td>10–40</td>
<td>1751</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>52–171</td>
<td>297</td>
<td>15–350</td>
<td>299</td>
</tr>
<tr>
<td>γ-Glutamyltransferase</td>
<td>12–64</td>
<td>140</td>
<td>8–61</td>
<td>104</td>
</tr>
</tbody>
</table>
Normal platelet count for children is between 150,000 to 450,000/µL. The patient presented with 92,000/µL. Which process is likely hindered in this patient?

A. Digestion  
B. Blood clotting  
C. Respiration  
D. Hormone production  
E. Glycogen metabolism
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Abdominal Ultrasound

- Mild, diffuse heterogeneous echotexture of the liver
- No intrahepatic or extrahepatic biliary ductal dilatation was noted
- The gallbladder was contracted, with no pericholecystic fluid and no ascites
- Enlarged spleen
- Normal upper abdomen results
Summary of Physical Examination and Laboratory Tests

Patient has:

- Acute hepatitis – inflammation of liver
- Hyperbilirubinemia – elevated levels of bilirubin in blood
- Leukopenia – low white blood cell count
- Lymphopenia – low lymphocyte count
- Thrombocytopenia – low platelet count
- Splenomegaly – enlarged spleen
Differential Diagnosis
Toxin Mediated Disease

- Acetaminophen overuse
  - Can lead to hepatitis (liver inflammation)
  - Acetaminophen reduces glutathione stores
    - Glutathione is a potent antioxidant, meaning it absorbs reactive oxygen species and prevents them from harming the liver
    - If glutathione is decreased, then the liver will take more insults and develop higher levels of inflammation
Toxin Mediated Disease

- Ingestion of the recreational drug Ecstasy
  - Also known as 3,4-methylenedioxymethamphetamine (MDMA)
  - Can lead to hepatitis (liver inflammation), nausea, vomiting, and jaundice
- Ingestion of the wild mushrooms *Amanita pantherina* or *Amanita muscaria*
  - Wild mushrooms that could be found in the wooded forest near the patient’s home
  - Can lead to nausea, malaise, and disorientation
  - Usually does not lead to jaundice or severe hepatitis

Fitting diagnosis?

- Acute hepatitis
Inherited Disease: Dubin–Johnson Syndrome

- Benign disorder characterized by jaundice – for most, jaundice appears during adolescence or early adulthood
  - Can cause weakness, mild abdominal pain, nausea, or vomiting
- Caused by mutation in the ABCC2 gene – expresses a protein that transports certain substances, like bilirubin, out of liver cells and into bile

Fitting diagnosis?

- Conjugated hyperbilirubinemia
- Family history of liver disease
Inherited Disease: Rotor Syndrome

- A mild condition characterized by hyperbilirubinemia
- Caused by mutations in both the $SLCO1B1$ and $SLCO1B3$ genes that express proteins that transport bilirubin from the blood to the liver’s bile

Fitting diagnosis?

- Conjugated hyperbilirubinemia
- Family history of liver disease
Inherited Disease: Wilson’s Disease

- Inherited disorder in which excessive amounts of copper accumulate in the body – liver, brain, eyes
- Liver disease is typically the initial feature in children and young adults
- Caused by mutation in ATP7B gene – role in transport of copper from liver to other parts of body

Fitting diagnosis?

- Conjugated hyperbilirubinemia
- Hepatosplenomegaly
- Family history of liver disease
Inherited Disease: Alpha$_1$-antitrypsin Deficiency (MZ phenotype)

- Inherited disorder that may cause lung and liver disease
- Mutations in the SERPINA1 gene – alpha-1 antitrypsin protects body from neutrophil elastase – fights infection but can attack normal tissues if not controlled
  - Three alleles: M - normal levels of protein, S - moderately low levels, Z - very low levels
- MZ phenotype – increased risk of impaired lung or liver function

Fitting diagnosis?
- Jaundice
- Family history of liver disease
- Acute hepatitis
For single-gene genetic disorders, there are several modes of inheritance. Which inheritance pattern results in disease at a higher frequency for males than for females?

A. Autosomal dominant
B. Autosomal recessive
C. X-linked dominant
D. X-linked recessive
E. Mitochondrial
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Infection: Hepatitis A, B, and C Viruses

- Viral infections of the liver that causes inflammation of the liver
- HAV: Acute, short-term disease. Commonly transmitted by food or water contaminated by feces of HAV infected person
- HBV and HCV: Chronic. Transmitted through contact with infectious body fluids - blood, vaginal secretions, semen
  - Commonly transmitted through injection drug use and sexual contact

Fitting diagnosis?

- Jaundice
- Acute hepatitis
Infection: Epstein-Barr Virus

- Also known as human herpesvirus 4
- Symptoms: fatigue, fever, inflamed throat, swollen lymph nodes (neck), enlarged spleen, swollen/inflamed liver, rash
- Can cause bone marrow suppression through development of Hemophagocytic lymphohistiocytosis (HLH)
  - Severe systemic inflammatory syndrome - results from excessive activation of immune system

Fitting diagnosis?

- Hepatitis
- Splenomegaly
- Low white blood cell and platelet counts
Infection: Lyme Disease

- Tick-borne disease caused by the bacterium *Borrelia burgdorferi*
- Symptoms: fever, headache, fatigue, rash, facial palsy, meningitis, and heart block
- Prevalent in deer ticks in the upper east coast and upper midwest

Fitting diagnosis?

- Patient lives in wooded area in New England
Infection: Human Granulocytic Anaplasmosis

- Tick-borne illness caused by the bacterium *Anaplasma phagocytophilum*
- Symptoms: headaches, fever, chills, myalgia, malaise
- Prevalent in deer ticks found in New England
- Lab indicators: low white blood cell count, low platelet count, elevated levels of specific liver enzymes

Fitting diagnosis?

- Patients lives in wooded area in New England
- Thrombocytopenia, leukopenia, elevated aminotransferase levels
Infection: Rocky Mountain Spotted Fever

- Tick-borne disease caused by the bacterium *Rickettsia rickettsii* often carried by the American dog tick
- Symptoms: fever, headache, rash, nausea, vomiting, stomach pain, muscle pain, and lack of appetite
- Lab results include: low white blood cell count, low platelet count, elevated levels of specific liver enzymes

Fitting diagnosis?

- Has two dogs and lived in a wooded area
- Thrombocytopenia, leukopenia, elevated aminotransferase levels
Aminotransferases or transaminases transfer amino groups between amino acids and keto acids. What are the products of the transamination of alanine?

A. Glutamate and oxaloacetate
B. Aspartate and α-ketoglutarate
C. Leucine and 2-oxoglutarate
D. Aspartate and pyruvate
E. Glutamate and pyruvate
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Autoimmune Hepatitis

- Exact cause unknown
- Chronic inflammation can lead to liver cirrhosis
- Family history of autoimmune disease
  - Second cousin diagnosed with lupus
- Associated with aplastic anemia
  - Acute Hepatitis
  - Conjugated hyperbilirubinemia
  - Cytopenia

Fitting diagnosis?

- Patient presents with elevated bilirubin, low WBC and RBC, high ALT/AST
Cancer

- Acute Leukemia
  - Associated with hepatomegaly and splenomegaly
  - Lymphadenopathy
  - Hematologic abnormalities
    - Platelet count <100,000/microL
    - Anemia (and pallor)
    - Low WBC in ~50% of cases

- Fitting diagnosis?
  - Hepatosplenomegaly
  - Hematologic abnormalities

- Hepatosplenic T-cell Lymphoma
  - Most patients with HSTL present:
    - Splenomegaly
    - Hepatomegaly
    - Thrombocytopenia
    - Anemia
    - Neutropenia
    - Abnormal liver function tests

- Fitting diagnosis?
  - Splenomegaly
  - Hepatic abnormalities
  - Thrombocytopenia
What do you expect the most likely cause to be?

A. Toxin-mediated Disease
B. Inherited Disease
C. Infection
D. Autoimmune Hepatitis
E. Cancer
Narrowing Down the Diagnoses
Possible Diagnosis: Toxin-mediated Diseases

Acetaminophen overuse

- While acetaminophen could be the cause of the hepatitis, it does not cause alteration of blood cell counts seen in the patient

Ingestion of ecstasy or wild mushrooms

- Does not cause alteration of blood cell counts seen in the patient

Conclusion: Highly unlikely cause of illness especially considering the patient stated they are drug-free.
COX-2 is an enzyme that produces prostaglandins which can cause pain and swelling during inflammation. Which of the following drugs is **NOT** a COX-2 inhibitor?

A. Acetaminophen  
B. Ibuprofen  
C. Naproxen  
D. Aspirin  
E. Piroxicam
COX−2 is an enzyme that produces prostaglandins which can cause pain and swelling during inflammation. Which of the following drugs is NOT a COX−2 inhibitor?

A. Acetaminophen  
B. Ibuprofen  
C. Naproxen  
D. Aspirin  
E. Piroxicam
Possible Diagnoses: Dubin–Johnson Syndrome and Rotor Syndrome

- The syndromes do not manifest with decreased cell counts or elevated aminotransferase levels
- Pruritus is uncommon for these conditions

Conclusion: The syndromes do not correlate with the patient’s presentation and lab results.
Possible Diagnosis: Wilson’s Disease

- In affected patients hepatitis does not resolve spontaneously - mother
- The disease usually manifests earlier in life
- The hepatitis is unlikely to be confused with nonalcoholic fatty liver disease – grandfather
- Bone marrow is not affected in affected persons
- Ceruloplasmin (ferroxidase enzyme – major copper-carrying protein) level was normal – can be normal in affected patients who have an acute inflammatory disease

Conclusion: The disease can be ruled out on the basis of family history and lab results.
Possible Diagnosis: Alpha-1 Antitrypsin Deficiency

- Affected patients often are not asymptomatic – more likely to have hepatitis in the context of concurrent illness
- Absence of family history of lung disease

Conclusion: The condition is an unlikely diagnosis. However, if hepatitis develops in other family members, it would be beneficial to get genetic testing for the condition.
Possible Diagnoses: Hepatitis (ABC) Viruses

- Serological tests reported negative results

Conclusion: Infection by these viruses is ruled out.
Possible Diagnosis: Epstein–Barr Virus

- Test was negative for heterophile antibodies, but in early stages of infection, the test is often negative
- Usually diagnosis of HLH is made if patients meets 5 of 8 criteria – patient met two – but other criteria not evaluated
  - Fever, splenomegaly, cytopenia, hypertriglyceridemia, hemophagocytosis, low or absent NK cell activity, elevated ferritin level in serum, and elevated soluble interleukin-2 (CD25) levels
- Physical examination not consistent with HLH and EBV – no fever, pharyngitis, or lymphadenopathy

Conclusion: EBV is a likely diagnosis for the patient as there is great variability of HLH presentation, but further testing would be needed
Pathogens are disease-causing microorganisms. Which pathogen is the smallest in size?

A. Bacteria
B. Fungi
C. Viruses
D. Dr. Freund
E. Parasites
Pathogens are disease-causing microorganisms. Which pathogen is the smallest in size?

A. Bacteria
B. Fungi
C. Viruses
D. Dr. Freund
E. Parasites
Possible Diagnosis: Lyme Disease

- Antibody testing for *B. burgdorferi* were negative
- Patient’s presentation is not consistent with Lyme disease

Conclusion: A unlikely diagnosis due to the patient’s presentation. Testing for Lyme disease can be done, but false positive results are common especially if affected with acute EBV infection.
Possible Diagnosis: Human Granulocytic Anaplasmosis

- Patient did not present common features of the disease – fever, headache, myalgia (muscle pain), and arthralgia (joint pain)

Conclusion: The patient’s lab results are typical for the disease, but blood nucleic acid testing for anaplasma would be needed to confirm.
Possible Diagnosis: Rocky Mountain Spotted Fever

- Affected patients are typically febrile and appear more ill than the patient
- Majority of patients have a rapidly progressive petechial rash

Conclusion: While the lab results are consistent with the disease, it is unlikely that the patient is afflicted with it.
Possible Diagnosis: Autoimmune Hepatitis

- Hemoglobin and RBC counts are low
  - However, levels are not declining at the rate for someone with aplastic anemia
- Patient presents with splenomegaly
  - Would not be caused by enlarged liver

<table>
<thead>
<tr>
<th></th>
<th>150,000–400,000</th>
<th>95,000</th>
<th>150,000–450,000</th>
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<tr>
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Conclusion: Lab tests and imaging do not match someone with this diagnosis
Possible Diagnosis: Hepatosplenic T-cell lymphoma

- Often manifests in a range of conditions, including the ones in this patient
- This condition is quite rare
- Median age at diagnosis is about 35 years old
- Occurs more commonly in immunosuppressed patients than in immunocompetent ones

Conclusion: Hepatosplenic T-cell lymphoma cannot be ruled out but it is less likely to be the cause considering how rare it is.
Possible Diagnosis: B-cell acute lymphoblastic leukemia

- Can be associated with hepatosplenomegaly and without lymphadenopathy
- Leukemia is the most common childhood cancer
- Some patients present with jaundice
  - Hyperbilirubinemia and elevated aminotransferase levels
  - This patient exhibited these symptoms
- Patients typically have low blood cell counts
  - Seen in this patient’s results
- Blasts may be scant or absent on a peripheral-blood smear

Conclusion: Likely based on symptoms and epidemiology
Final Diagnosis
Final Diagnosis

B-cell acute lymphoblastic leukemia
Pathology of B–cell acute lymphoblastic leukemia
Flow cytometry
Genetics of B-cell acute lymphoblastic leukemia
What do you think the best treatment is for this patient?

A. Surgery
B. Antibiotics
C. Chemotherapy
D. A and C
E. None of the above
What do you think the best treatment is for this patient?

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B. Antibiotics
C. Chemotherapy
D. A and C
E. None of the above
Treatment

Started a treatment of 4 chemotherapy drugs

- Prednisone
- Vincristine
- Daunorubicin
- Polyethylene glycol-asparaginase

Bilirubin levels were checked periodically

Higher doses of chemotherapy drugs were administered as bilirubin levels fell
Vincristine prevents microtubule assembly. What cellular function is this most likely to affect in cancer cells?

A. Phagocytosis
B. Cell–Cell Adhesion
C. Cell Migration
D. Chromosomal Segregation
E. Cilia Formation
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Resolution/Updates

- Chemotherapy treatment lasted for 29 days
- Methotrexate administered in cycles following treatment
  - Lasted 39 months
  - No complications
- Almost 4 years after diagnosis, the patient is well and in complete remission
Clinical Relevance

- This case is particularly interesting due to the young age of the patient
  - Regarded as an extremely high risk case for displaying symptoms of Acute Lymphoblastic Leukemia (ALL) at 16
- Great example of why you must analyze all of the lab results together to come to a proper diagnosis
  - While ALL is the correct diagnosis, it generally would not be the first diagnosis for a child presenting with malaise, jaundice, and fatigue
  - Much more likely diagnosis is viruses or gallstones
  - Only by analyzing the blood cell counts could they diagnose leukemia
Questions?
Sources

- https://www.heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings
- https://www-uptodate-com.proxy2.library.illinois.edu/contents/search
- https://www.healthline.com/health/hepatitis#symptoms
- https://www.cdc.gov/epstein-barr/about-ebv.html
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