Lecture 2[2hrs]

(3) Obstructive jaundice [Cholestasis].

*Failure of bile flow**.**

*The cause of cholestasis can arise anywhere in the biliary system.

These conditions characterized by predominant elevation of serum bilirubin and alkaline phosphatase levels relative to aminotransferase levels

causes of cholestasis include

A-intrahepatic Cholestasis-

Hepatocyte dysfunction and impaired transport of bilirubin to the bile canaliculi.

causes include

*Infiltrative diseases:

*Granulomatous disorders of the liver: include--infections (tuberculosis, syphilis, parasites, fungal diseases, leprosy, and brucellosis).

*Drugs (allopurinol, sulfonamides, and quinidine).

*Systemic disorders (Sarcoidosis, Wegner'sgranulomatosis, and Hodgkin lymphoma).

*Systemic amyloidosis, which can present with hepatomegaly, jaundice, macroglossia, heart failure, renal failure, and intestinal malabsorption.

Disorders involving the biliary ductules: include

*Primary biliary cholangitis is characterized by inflammation of the small intrahepatic bile ducts and occurs primarily in middle-aged women.

*Graft-versus-host disease occurs in up to 10% of bone marrow transplant recipients.

*Drug-induced cholestasis: either 'bland' cholestasis or in some cases accompanied by features of immunoallergy including arthralgia's, fever, and rash in addition to peripheral eosinophilia.

Medications That can cause cholestasis includes

*Estrogen, anabolic steroids, erythromycin, amoxicillin–clavulanic acid, trimethoprim-sulfamethoxazole, antifungal Terbinafine, oral contraceptives, clopidogrel and tricyclic antidepressants mirtazapine and total parenteral nutrition.

B-Extrahepatic Cholestasis.

Obstruction of the extrahepatic bile ducts.

Causes

*Diseases of the bile ducts,

*Extrinsic compression or Occlusion of the bile duct lumen.

Diseases of the bile ducts include:

*Congenital disorders such as choledochal cysts and biliary atresia.

*Inflammatory disorders such as primary sclerosing cholangitis.

*Infectious disorders such as acquired immunodeficiency syndrome (AIDS) cholangiopathy. Cholangiocarcinoma.

Extrinsic Compression of the bile ducts include

*Pancreatic carcinoma, *Hepatocellular carcinoma,

*Ampullary adenoma and lymphoma.

*Choledocholithiasis

Clinical Approach to Jaundice

History should include

*The onset, duration of jaundice and associated symptoms Like

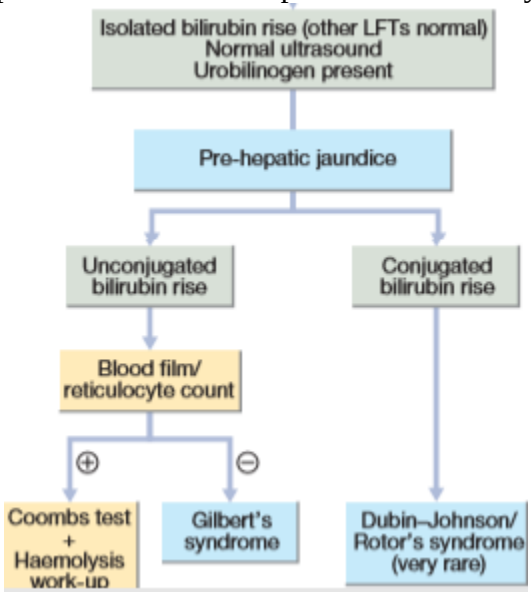
*Fatigue, abdominal pain, nausea, vomiting, fever or chills,

*Weight loss, arthralgia or arthritis.

*Patients with cholestasis also may develop pruritus.

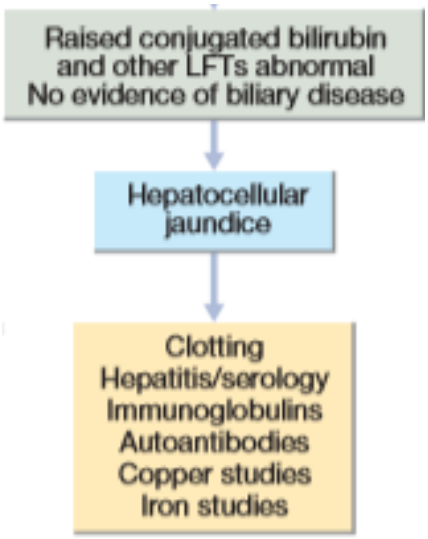
*Recurrent abdominal pain and nausea may indicate (gallstones).

*Epigastric pain radiating to the back with weight loss and gallbladder distention may indicate (pancreatic head carcinoma).
*History of drug use, alcohol abuse, blood transfusions, unprotected sex.
*Family history of liver or pancreatic disease.
*The past medical and surgical history should identify disorders associated with jaundice such as hepatobiliary disease, hemolytic anemia (e.g., sickle cell disease), AIDS, inflammatory bowel disease, and previous biliary surgery.
The physical examination should focus on signs of systemic infection like (fever, tachycardia, tachypnea),
*Xanthelasma and xanthomas occurs in prolonged cholestasis
*Stigmata of Chronic liver disease include (ascites, spider telangiectasias, palmar erythema, gynecomastia and testicular atrophy in men, hepato-splenomegaly, encephalopathy)
*Sings of heart failure.
A diagnostic approach for jaundice
1-*Elevated serum bilirubin, normal liver enzyme, and the US. This indicates
Pre hepatic jaundice
*Elevated Unconjugated bilirubin, normal blood film and Retic count this is Gilbert syndrome. *Conjugated Hyperbilirubinemia, normal blood film and Retic count this indicate Dubin-johnson or Roters syndrome
*High Retic count and positive Coombs test patient need hemolysis workup.



A diagnostic approach for Pre hepatic jaundice

2-* Hepatocellular jaundice. *investigations shows raised bilirubin, elevated liver function tests, and normal Us
Laboratory Studies include
*Viral serology's for hepatitis, A.B.C.D, E
*Serum levels of iron, transferrin, and ferritin for hemochromatosis.
*Serum ceruloplasmin copper,24 hrs. urine for copper (for Wilson disease),
*Antimitochondrial antibodies (for primary biliary cholangitis),
*For autoimmune hepatitis= antinuclear antibodies, smooth muscle antibodies, LKM antibody, and serum protein electrophoresis or serum immunoglobulin's
*Alfa fetoprotein

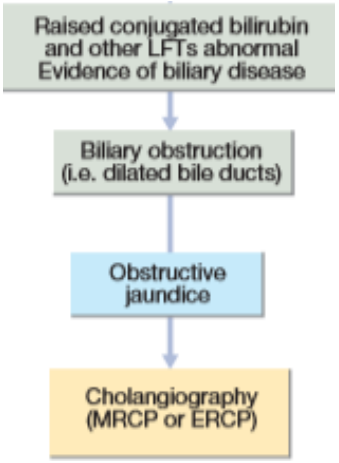


A diagnostic approach for hepatocellular jaundice

3*-Biliary Obstruction -*investigations shows Hyperbilirubinemia, abnormal liver LFTs and the US shows evidence of biliary disease patient should undergo further evaluation with*Magnetic Resonance Cholangio-Pancreatography (MRCP)if dilated bile ducts this means

Patients' needs

*Endoscopic Retrograde Cholangio-Pancreatography (ERCP for therapeutic intervention to relieve the biliary obstruction.



A diagnostic approach for obstructive jaundice

A liver biopsy may be necessary for patients with abnormal liver enzymes without evidence of biliary obstruction and obscure diagnosis

Treatment

The management of the patient with jaundice depends on the cause.

*When jaundice is caused by liver disease, management should be directed toward the underlying cause.

*Elevation of unconjugated bilirubin in neonates and infants has the potential to cause kernicterus with irreversible brain injury and should be treated promptly with Phototherapy which reduces the risk of neurotoxicity by making bilirubin more water-soluble. Or exchange blood transfusion in severe cases.

*If drug-induced cholestasis is suspected, all potential drugs should be discontinued and the patient observed for resolution of symptoms.
*Treatment of parenchymal liver disease will be discussed later
*Patients with biliary tract obstruction due to Choledocholithiasis or malignancy need endoscopic or surgical intervention to restore adequate biliary drainage.
*****Pruritus -can be treated with antihistamines, rifampin, bile acid-binding resins [cholestyramine].
*****Steatorrhea - malabsorption of fat and fat-soluble vitamins (A, D, E, and K) can be managed by a reduction in oral fat intake and substitution of dietary fat with medium-chain triglycerides and Vitamin supplements

Unusual Forms of Cholestasis include

1-Recurrent intrahepatic Cholestasis in pregnancy:
*Autosomal recessive inheritance condition caused by inherited susceptibility of liver cells to estrogens may be precipitated by oral contraceptives

Clinical Features include-
*Itching starts in the 3rd trimester of pregnancy and remit within 2 weeks of delivery.
*Jaundice occurs in about half of the patient,
*Condition tends to occur in subsequent pregnancies.
The main complications are prematurity, increased risk for neonatal respiratory distress syndrome.

investigations
*Elevation of bile acids, ALP, conjugated Hyperbilirubinemia, and GGT is low.
Treatment-Cholestyramine, Ursodeoxycholic acid, Fat-soluble vitamins

2-Benign Recurrent Intrahepatic Cholestasis [BRIC].
*Autosomal recessive inheritance Disease
*Characterized by Intermittent episodic cholestasis lasting from 1-6 m.
*Episodes start with Pruritis and painless jaundice.
*Liver function tests show the pattern of cholestasis during an episode and normal between episodes.
*Genetic factors may be important as any family member may be affected.
*Long term prognosis is good**.**

Hepatomegaly

*Hepatomegaly is a physical sign on abdominal examination.
*Assessment of liver size is important in diagnosing liver disease. Start palpation in the right iliac fossa, Progress up the abdomen 2 cm with each breath (through the open mouth), Confirm the lower border of the liver by percussion. Detect if smooth or irregular, tender or non-tender; ascertain the shape, Identify the upper border by percussion.
*The normal liver extends from 5TH intercostal space in the mid-clavicular line down to the costal margin.

When the liver is palpable this may be due to:
(1) increased diaphragmatic descent.
(2) Presence of a palpable caudate or Riedel's lobe [downward tongue-like projection of the right lobe of the liver.
(3) Presence of emphysema with an associated depressed diaphragm;
(4) Thin body habitus with narrow thoracic cage;
(5) Fatty infiltration (enlarged with a rounded edge);
(6) Active hepatitis (enlarged and tender);

(7) Cirrhosis often presents with hepatomegaly (enlarged with nodular irregularity although in end-stage disease the liver may be reduced in size.
cirrhosis with hepatomegaly it is more common in alcoholic liver disease and hemochromatosis
(8) Hepatic neoplasm (enlarged with rock-hard or nodular consistency).
(9) Right-sided heart failure occurs because of hepatic venous congestion secondary to impaired myocardial function causing (hepatomegaly with smooth surface).
(10) Primary and secondary liver tumors', hepatobiliary disease, and hematological disease.

Parenchymal Liver Disease

Acute hepatitis means a recent sudden injury to the liver. Acute hepatitis is usually self-limited. Some patients may progress to fulminant liver failure or gradually evolves into chronic hepatitis with inflammation persisting more than six months and may be accompanied by fibrosis and progression to cirrhosis with PHT and its complications.

Viral Hepatitis

*There are five major hepatotropic viruses (viruses that have an affinity for hepatocytes): These include hepatitis A virus (HAV); hepatitis B virus (HBV); hepatitis C virus (HCV); hepatitis D virus (HDV) and hepatitis E virus (HEV).
All hepatitis viruses are RNA viruses except for HBV which is a partially double-stranded DNA virus.

1-Hepatitis A Virus [HAV]

*Hepatitis A virus (HAV) is a non-enveloped RNA enterovirus.
*Endemic in underdeveloped countries
*Transmission of HAV is by the fecal-oral route.
*The group most affected is aged 5 – 14 yr.
usually subclinical or passed as gastroenteritis in children
*Hepatitis A virus reaches the liver through portal circulation and primarily infects hepatocytes
*HAV replicates within the cytoplasm of hepatocytes and viral particles produced are excreted through the biliary tract into the feces.
*The incubation period is 15-50 days and the acute illness lasts two to three weeks.
*The virus is present in the stool of patients from the Prodromal or pre-icteric phase to about 2 weeks after the onset of jaundice. Transmission can occur during this time. *There is a brief period of viremia during the acute phase of infection and parenteral transmission can occur following transfusion of blood during viremia of acute infection.

Clinical features include
*Flu-like symptoms such as malaise, fatigue, anorexia, fever, aversion to food, and smoking.
*Jaundice may be mild to moderate.
*Hepatitis A never causing chronic hepatitis.

The Spectrum of Clinical Manifestation of Hepatitis A include:
1- Asymptomatic disease without jaundice.
2- Symptomatic, self-limiting disease with jaundice for less than 8 weeks.
3 -Cholestatic jaundice lasting more than 10 weeks.
4 -Relapsing acute hepatitis with two or more instances over 10 weeks.
5 -Acute hepatic failure.

Investigation.
*Elevated liver enzymes [AST, ALT] and serum bilirubin.

*IgM anti‑HAV antibodies appear within 5 to 10 days before symptoms or at the early phase of ALT elevation and become undetectable at six months but the IgG persists for life.

Complications include

*Acute liver failure.

*Cholestatic phase -deep jaundice and itching may last 3m followed by complete recovery,

* Relapsing hepatitis within 1 m to 3 m.

Extrahepatic complications related to vasculitis and immune complex disease like

*Aplastic anemia, *glomerulonephritis *myocarditis and *cryoglobulinemia.

Treatment

*Treatment of the active disease is supportive.

*Most cases can be managed on an outpatient basis.

*Strict bed rest is not necessary.

*Encouraging a high-calorie intake.

*Fatty foods are poorly tolerated and better to be avoided.

*All unnecessary drugs especially tranquilizers and sedatives should be avoided.

*Prednisolone 30 mg for 2-3 w may be used for Cholestatic hepatitis.

Prevention of HAV include

*Handwashing.

*Passive immunization-The serum immune globulin protects if given 0.02mL/ kg before exposure or 0.06mL/ kg within two weeks of exposure.

*Active immunization - hepatitis A vaccine is used for disease prevention. vaccines are administered in two doses. It is recommended in persons above the age of 2 years in communities with high rates of hepatitis A. The most common side effect of the vaccine is pain at the site of injection.

2-Hepatitis E Virus [HEV].

*Hepatitis E (HEV) is caused by a single-stranded RNA virus.

*Hepatitis E virus occurs in countries with poor sanitation.

*The incubation period is15-60 days.

*HEV infection causes self-limited hepatitis and does not cause chronic infection only in immunocompromised patients and especially in organ-transplant recipients, although this remains uncommon.

Transmission through contaminated food and water.

Clinical features include

*Malaise, fever, nausea, vomiting, anorexia, abdomen discomfort and headaches, *jaundice lasting seven to 12 days.

*Liver enzymes may be elevated for one to two months.

*HEV associated with a high mortality rate (approaching 20%) in infected pregnant women in the third trimester the reason is unclear.

Diagnosis

Serological assay anti-HEV (IgM or IgG), HEV RNA assay

Treatment

*Supportive as the disease appears mild and self-limited

*Liver transplantation for fulminant hepatic failure.

Prevention

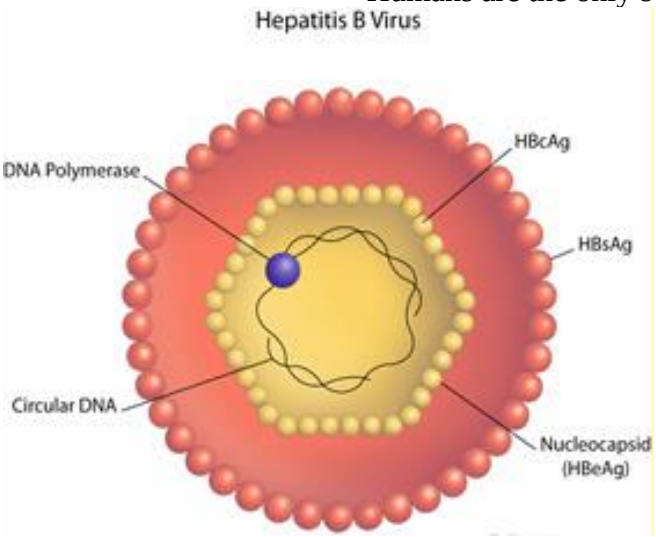
*There is no active or passive immunization for HEV.

*Avoiding uncooked food or untreated water.

*Hand-washing before eating and no swimming in polluted water.

3-Hepatitis B Virus[HBV]

*The hepatitis B virus consists of a core containing DNA and a DNA polymerase enzyme needed for virus replication.
*The core of the virus is surrounded by hepatitis B surface antigen [HbsAg].
*The virus, also called a Dane particle.
*Humans are the only source of infection.



*HBV is a hepatotropic virus that replicates in the liver and causes hepatic damage and dysfunction
*HBV is a small encapsulated DNA virus that replicates through reverse transcription of its mRNA.
*Eight genotypes of HBV (A–H): differing from one another in genome sequencing.

Mode of Transmission of HBV.

*The primary mode of transmission of HBV is by Blood and blood products
*Tattooing or acupuncture, ear piercing, manicures *sexual transmission
*Vertical transmission of HBV from mother to newborn.
*Transmission of HBV may occur by contaminated instruments or accidental needle sticks.
*HBV is 10 times as infectious as HCV and 100 times as infectious as HIV.
*HBV can survive outside the body for at least 7 days during that time the virus can cause infection if it enters the body of a person who is not infected.
*HBV is not spread by contaminated food or water
*Breastfeeding is acceptable and does not pose a risk of transmitting HBV to infants.

Hepatitis B can cause both acute and chronic hepatitis.

*The age at infection determines the rate of progression from acute hepatitis to chronic hepatitis.
* 90% in the perinatal period.
*20-50% in children aged 1-5 years.
* < 5% in adults

.

Acute Hepatitis B

*The incubation period ranges from 60-110 days**.**
*Prodromal symptoms usually precede the development of jaundice by days to weeks.

Clinical features include - Fever, Headache, Malaise, Anorexia, Nausea, Vomiting, diarrhea, Arthralgia, and Upper abdominal pain. Smokers may find tobacco tastes bad.

Physical Signs:- liver Tenderness, Enlarged cervical LN, Splenomegaly may occur, Jaundice, Skin rashes (serum sickness), Polyarthritis, and Dark urine.

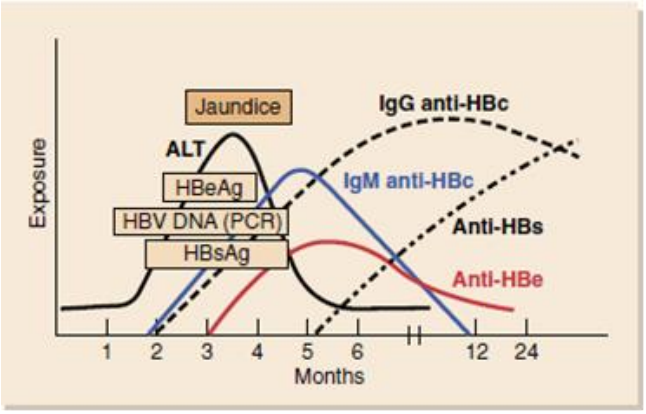
Diagnosis of Acute HBV infection

*Elevated liver enzyme with hyperbilirubinemia.

*The first serologic marker to appear in acute HBV is HbsAg 1–6 weeks before the onset of symptoms.

*IgM anti-hepatitis B core (anti-HBc) appears 1–2 weeks after HbsAg. But there may be window period where both anti-HBS and HBsAg are negative, leaving anti-HBC-IgM the only detectable marker.

*Recovery from acute hepatitis B characterized by the development of [anti-HBs Ab, anti-HBc IgG Ab and disappearance of HBsAg.]



Serologic responses to hepatitis B virus infection

Treatment of Acute Hepatitis B.

*Supportive care is sufficient in the majority of patients.

*There is no need for antiviral treatment because most acute infections clear completely

*Indications for antiviral therapy in acute HBV infection: fulminant hepatitis, hepatic encephalopathy, INR > 1.6, protracted course (elevated bilirubin > 10 mg/dL for > 4 weeks), immunocompromised patients, coexisting hepatitis C or other chronic liver disease.

*Interferons should be avoided. Treatment with any of the oral antivirals is appropriate lamivudine, tenofovir, entecavir is indicated and continued until the disappearance of HBs Ag.

*Ffulminant hepatitis may need liver transplantation**.**

Prognosis

The overall mortality for acute viral hepatitis is about 0.5% inpatient under 40 years of age and 3% mortality for the patient above 60 years.

Chronic Hepatitis B

*Means persistence positive HBsAg for greater than six months.

*Chronic hepatitis B can be divided into HBeAg positive and HBeAg negative.

*Chronic hepatitis B may be accompanied by fibrosis and progression to cirrhosis with PHT and its complications**.**

The Natural Course of Chronic HBV infection [CHBV**].**

*Chronic HBV infection is a dynamic process that can be divided into five phases these are not necessarily sequential, however and not all patients will go through all phases

1-Immune Tolerant Phase: characterized by –

*HBeAg positive, *High HBV DNA, *normal aminotransferases,

*Mild necro-inflammation on liver biopsy.

*Highly contagious. *Usually occurs with infection acquired in childhood.

*May seroconvert spontaneously (loss of HBeAg and HBsAg).

2-Immune Reactive Phase: characterized by –

*HBeAg positive, * lower HBV DNA, *Fluctuating aminotransferases, *Moderate necro-inflammation on liver biopsy* Higher risk of fibrosis.

*Usually occurs when infection acquired in adulthood •

3-HBeAg Negative CHBV Phase: characterized by- *HBeAg negative, *anti-HbeAb positive, *fluctuating HBV DNA >1000 IU/mL, *fluctuating aminotransferases.

*High risk of progressive fibrosis and cirrhosis.

4-Inactive Carrier Phase-characterized by

*HBeAg negative and *anti-HBe positive

*Undetectable or low serum HBV DNA *Persistent normal ALT.

*Liver biopsy shows the absence of significant necro-inflammation

5-Occult HBV infection:

*HBsAg negative,

*Low HBV DNA (<200 IU/mL) a

*Presence of markers of previous infection anti-HBc total/or anti-HBs positivity

*May be associated with fibrosis progression and development of HCC.

It is important to remember that the virus is not directly cytotoxic to cells; rather it is an immune response to viral antigens displayed on infected hepatocytes that initiate liver injury. This explains why there may be very high levels of viral replication but little hepatocellular damage during the immune tolerance phase.

However, clearance of HBsAg does not exclude the development of cirrhosis or hepatocellular carcinoma even in the absence of inflammation and fibrosis because HBV integrates into host hepatocyte DNA.

The Clinical Presentation -

*May be asymptomatic or presented with * unexplained fatigue or

*Presented with stigmata of CLD such as splenomegaly, spider angiomata. caput medusa, palmar erythema, testicular atrophy, gynecomastia. With or without signs of decompensated cirrhosis Like [- jaundice, ascites, peripheral edema, and encephalopathy.]

*About 10-20% of patients presented with extrahepatic manifestations of chronic hepatitis B infection like

*Glomerulonephritis*Essential mixed cryoglobulinemia.

*Palpable purpura and acrodermatitis. *Polyarteritis Nodosa.

Investigations

Testing for HBV can be divided into

*Serologic tests for detection of antibodies and antigens include_HbsAg, Anti-HBs, HBeAg, Anti-Hbe, Anti-HBc [lgM, lgG]

*Molecular test for detection of HBV DNA Viral load by PCR

*Liver function test include

*Albumin, total protein, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels, PT]

*CBC, Renal function, abdominal US

*Assessment of liver fibrosis by liver biopsy or by non-invasive tools such as liver Fibroscan or Fibrotest.

The Significance of HBV Markers and Their importance in the interpretation.

 HBs Ag – indicate marker for acute or chronic infection.
 HBs Ab – indicate Immune to HBV [as natural immunity or after HBV vaccination].
 HBc Ab-IgM-indicate Acute HBV infection or reactivation of chronic infection.
 HBe Ag –indicate High infectivity and viral replication.
Ø HBe Ab-indicate Low infectivity.
 HBV-DNA-Measure of infectivity or replicative state.

Seromarkers of HBV infection

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc
Acute HBV	+	–	+	–	IgM
Chronic HBV (high infectivity)	+	–	+	–	IgG
Chronic hepatitis[low infectivity)	+	–	–	+	IgG
Recovery	–	+	–	+	IgG
Immunization	–	+	–	–	–