CHAPTER 13 - JAUNDICE

BACKGROUND HEPATIC PHYSIOLOGY

Haemodynamics

Total hepatic blood flow is 1.5 litres per minute, two thirds from the splanchnic area (haemoglobin 85% saturated with oxygen) and one third from the hepatic artery. Lymphatics drain liver at the hilum with the flow rate of 0.7 ml/minute and a protein content very nearly equal to plasma. One fifth of the total pool of albumin passes daily through the hepatic lymphatics.

BROAD FUNCTIONS OF THE LIVER

We need to consider this as background, because derangement in function will determine the abnormalities seen in liver disease.

1. **Storage Functions.** Mostly relate to carbohydrate viz. glycogen.

2. **Role in Digestion** - particularly formation of bile salts for emulsification of fat.

3. **Role in intermediary metabolism.** All absorbed food passes first through the liver via the portal vein (except for chylomicrons; they travel via thoracic duct to systemic circulation). Liver drains pancreas and gut blood direct, which means that the liver cells are exposed to about 300 times the systemic concentration of insulin and other gut-derived polypeptide hormones. Insulin permits the liver to utilise glucose. The liver stores of glycogen are important in any state of hypoglycaemia. Interconversion of metabolic fuels occurs in the liver as well as urea synthesis from ammonium.

4. **Synthesis of various normal bodily substances.**

   (a) **Protein:** Liver is the important of plasma albumin. Daily synthesis about 12 grams. This becomes important in limiting the degree of fall in plasma albumin in any (non-hepatic) hypo-albuminaemic state, e.g. nephrotic syndrome.

Other circulating proteins synthesised include transferrin, and steroid-binding globulins.
(b) **Coagulation Factors.** Liver synthesises a number of factors important in the intrinsic coagulation pathway including Factors II (prothrombin), V, VII, IX and X, all by a vitamin K dependent pathway (except for V).

Fibrinogen is also synthesised in the liver, but this is not vitamin K dependent.

c) **Cholesterol synthesis.** HMG-CoA reductase is a rate-limiting step, and inhibition of this enzyme is the way the statins work to lower plasma cholesterol.

5. **Hormone metabolism**

Includes inactivation of insulin, thyroxine and steroid hormones (also aldosterone, oestrogen).

6. **Secretion of endogenous materials and exogenous drugs/toxins** into the gut

(a) **General**

The liver cells have a great deal of smooth endoplasmic reticulum (SER) and biochemically this "microsomal" fraction is extremely reactive. Its major functions are to conjugate (with glucuronate, glutathione, other amino acids, sulphate) and "oxidate" substances to be excreted. Oxidations are particularly important and are referred as mixed function oxygenations (MFO's). The term MFO arises because oxidation and reduction proceed together, and the reactions are oxygenations because molecular oxygen is incorporated into substrate. The MFO pathways have low substrate specificity and metabolise steroids, bile acids, and foreign chemicals from the gut as well as numerous drugs. Different substrates may compete for metabolism. Importantly, the activity of these systems is inducible to greater function (e.g. by drugs such as phenytoin, phenobarbitone).

(b) **Bile Metabolism - Important.**

Before we can begin to understand jaundice, we must have a good background knowledge of bile pigment metabolism.

Approximately 5 grams of haemoglobin are degraded per day. This yields 175 mg of haem to be excreted as bile pigment from the worn out red cells.

Unconjugated bilirubin is the end product of haem breakdown in the tissues. The first step is the removal of the haem prosthetic group from haemoglobin, and this occurs in the reticulo-endothelial cells of the tissues, largely in the spleen and bone marrow. This conversion involves oxidation of haem in the macrophage microsomal enzymes, with the release of iron, to form biliverdin. The latter is then reduced to bilirubin by a soluble cell enzyme. The capacity to make bilirubin from haem in this way is large and seldom unable to keep pace with the rate of breakdown of red cells. Therefore, rarely free haemoglobin in blood, unless very severe haemolysis.
Unconjugated bilirubin formed in the tissues is both water insoluble and toxic to cells, so there has to be a highly efficient mechanism for its removal. This is done by a high-affinity binding to plasma albumin, which can pull bilirubin out of tissues with great avidity.

On reaching the liver, bilirubin is stripped from albumin and taken up by the liver cells by a carrier-mediated transport system. Within liver cells, bilirubin is made water-soluble by conjugation with glucuronic acid under the influence of the enzyme glucuronyl-transferase. This process of **conjugated bilirubin pigment formation** is partly dependent on bile salts.

After conjugation, bile pigments and bile salts enter the gall bladder, and then the gut. The bile salts, having done their job of fat emulsification are re-absorbed in the terminal ileum. Because of their polarity, the conjugated bile pigments through pass most of the the small bowel unabsorbed; in the lower ileum and large gut, however, bacteria convert the bilirubin to stercobilinogen in the bowel. The small amount formed in the terminal ileal is reabsorbed to be returned via an entero-hepatic circulation to the liver, which normally re-excretes it again. If, as in some hepatic diseases, the liver is not able to re-excrete stercobilinogen back into the bile, this compound will accumulate in increasing concentrations in the plasma and spill over into the urine, where it is referred to as urobilinogen. Only about 20% of gut stercobilinogen is reabsorbed from the large bowel to partake in this enterohepatic circulation, and that which is not, is oxidised to stercobilin (urobilin), to impart the brown colour to the stool.

Accumulation of either conjugated or unconjugated bile pigment in the plasma for any reason (see below) causes clinical jaundice, best seen by examining the sclerae in natural light.

Accumulation of bile salts (e.g. from blockage of the passage of bile from bile ducts to the duodenum), causes a fat malabsorption steatorrhoea with reduced fat-soluble vitamin and cholesterol absorption from the gut; clinically, bile salt retention is also characterised by pronounced itch.

**CLINICAL JAUNDICE - A. ANATOMICAL DIAGNOSIS:**

This can be achieved in most cases from the history and physical examination, provided you pay sufficient attention to detail, analyze the urine for both bile pigment and excess urobilinogen (a small amount of urobilinogen is normally present in the urine), and look at the colour of the faeces. As usual, we must take an *hierarchic* approach to Anatomical diagnosis (mostly using information gained from our Functional diagnosis).

There are THREE BROAD ANATOMICAL LEVELS we need to consider, namely whether the jaundice is PRE-HEPATIC (increased production of bilirubin from increased breakdown of red blood cells), HEPATIC JAUNDICE (inability of the liver to process and pass on the bilirubin to the gut); and POST-HEPATIC (common bile duct obstruction) jaundice.
Before we can finally separate even these three broad categories, there is one final piece of information we need to know about bile metabolism in abnormal states. Unconjugated bilirubin formed in the periphery from red cell breakdown is water insoluble and tightly bound to albumin. As such, it is effectively transported through the circulation (until conjugated and excreted by the liver) as a large molecule the same size as albumin (MW = approx. 70,000). Thus, it is too large to be filtered through the glomerular capillaries, and this is why unconjugated bilirubin does not normally appear in the urine. By contrast, when for some reason (either blockage of the bile flow from the liver or some liver cell abnormality affecting transportation of conjugated bilirubin into the bile), conjugated bilirubin accumulates in the blood, this, being water soluble and non-protein bound, retains its small molecular weight - easily small enough to pass through the glomerular capillaries into the urine.

We are now in a position to diagnose the anatomical level of any jaundice on clinical grounds.

1. PRE-HEPATIC JAUNDICE

By this is meant increased production of haem pigment, almost always due to increased red cell breakdown. In such cases, the level of circulating (unconjugated) bilirubin increases. However, except in cases of very severe haemolysis, and provided liver function is normal, the liver can cope with the increased amount of unconjugated bilirubin presented to it by excreting more in the bile, and so pre-hepatic or haemolytic jaundice is not usually associated with an increase in plasma bilirubin of more than about 4-6 times normal.

Because the liver is producing more bile pigment, more stercobilinogen will be produced in the large bowel, which has two consequences. First, more will be reabsorbed, and because the entero-hepatic circulation of this pigment normally works at near maximum capacity, stercobilinogen (or urobilinogen as we usually call it) will accumulate in the blood. And, being a small molecule this urobilinogen will spill over into the urine (patients may then notice an orange or "black-tea"colour to the urine - urobilin). In addition, a greater quantity of stercobilinogen will appear in the stool, causing it (as stercobilin) to darken the stool. The bile pigment itself, being unconjugated, does not appear in the urine (acholuric jaundice).

As well as signs resulting from increased haem breakdown, there will usually be other signs related to the haemolytic process per se. First, the patient will usually be anaemic. In mild to moderate forms of haemolysis, most of the red cell breakdown occurs in the spleen and this gives rise to splenomegaly. On investigation, the blood reticulocyte count will be usually increased, and the red cells may give a clue in their shape to the abnormality which predisposes them to haemolysis e.g. spherocytes in congenital haemolytic anaemia. Also, as well as haem production, haemolysis produces increased globin, which binds to hapto-globins to form a complex normally rapidly cleared from the circulation, so reducing haptoglobin levels in the blood.
2. HEPATIC JAUNDICE

As expected, some of the retained bilirubin is of the unconjugated type in most liver disease. But one of the liver's important tasks is to transport bilirubin from the blood to the bile and, as we have seen, bilirubin is conjugated in the process. Now, most sorts of liver disease involve at least some element of impairment of bile transport once conjugated, so most of the bile pigment accumulating in the blood is conjugated bilirubin. This, being water soluble (and therefore not protein bound), is rapidly filtered at the glomerulus to appear in the urine.

Thus, hepatic jaundice is usually associated with some bile pigment in the urine. Also, in the absence of extensive obstruction to the small bile duct canaliculi within the portal tracts, some bile pigment does get through the liver in most hepatic disease, albeit in reduced amount, and continues on into the large gut, where it is converted to stercobilinogen/urobilinogen. As usual, some of this (reduced amount of) stercobilinogen carries into the stool to give it a darkish appearance; and, some is re-absorbed in the normal way. But in the presence of liver disease, the stercobilinogen now being presented back to the liver from the portal vein via the enterohepatic circulation, exceeds the ability of the liver to handle it, so the level of plasma stercobilinogen rises (the entero-hepatic circulation of stercobilinogen normally operates near a maximum). And this, being water soluble and nonprotein bound, therefore accumulates in the urine (now called urobilinogen) in excess quantity, together with the conjugated bilirubin. Hepatic causes of jaundice are therefore typically associated with both bile pigment and excess urobilinogen in the urine.

In addition to the above features, the classical case will show the functional evidence of the primary liver disease underlying the jaundice, particularly in chronic liver disease. Here again, our functional abnormalities give good clues to the primary site of anatomical involvement. We can think of these signs of hepatic dysfunction by reference to the broad principles of its normal function outlined above.

EVIDENCE OF HEPATIC DYSFUNCTION

(a) **Failure to produce usual quantities of normal substances.**

Reduced albumin production results in oedema, and contributes to ascites. However, the latter requires not only reduced production of albumin by the liver, but also portal venous hypertension &/or increased resistance to blood flow at the hepatic sinusoidal level - as commonly occurs in cirrhosis and other chronic liver diseases which destroy the normal hepatic acinar unit architecture.

Hyperaldosteronism secondary to both reduced 'effective' blood volume from reduced plasma albumin concentration and reduced hepatic aldosterone clearance also plays a part in oedema...
formation. Hypoalbuminaemia in liver disease is often also contributed to by an associated poor protein intake, particularly in alcoholics. Note, too, that the half-life of albumin in plasma is about 17 days, so it is relatively unaffected by acute liver disease (contrast prothrombin time - see below).

(b) **Reduced levels of the intrinsic clotting factors** will also occur including factors I (fibrinogen), II (prothrombin), V, VII, IX and X, and **easy bruising** may follow. Production of all of these except Factors I and V requires vitamin K, but in this situation it is the liver cell mechanism for producing prothrombin which is at fault, so no amount of even parenteral vitamin K can be expected to cause any improvement in prothrombin time (contrast Vitamin K malabsorption in obstructive jaundice - see below).

Biochemically, we assess blood clotting by the prothrombin time (expressed as INR - International Normalised Ratio) which is sensitive to levels of factors II, V, VII and X, particularly VII in acute cases, because this has the shortest half life (4-6 hours compared with more than a day for all the rest). It is evident from the above that **INR and plasma albumin** help not just the Functional Diagnosis but the Pathological Diagnosis as well.

(c) **Failure to Conjugate and Excrete Steroids.**

(i) **Aldosterone** is normally cleared by the liver and a decreased aldosterone clearance may therefore contribute to the increased plasma aldosterone associated with chronic liver dysfunction (secondary hyper-aldosteronism). This, in turn, contributes to the oedema and ascites discussed above, and lowers plasma potassium; hence aldosterone antagonists, e.g. spironolactone, may be useful in control of sodium retention/hypokalaemia in liver disease.

(ii) **Cortisol** excretion may be impaired and so some patients with hepatic dysfunction develop Cushingoid features.

(iii) **Oestrogens** are not cleared adequately in the presence of liver dysfunction and this contributes to feminisation in the male, in particular gynaecomastia, loss of bodily hair with reversion to a female hair distribution, and testicular atrophy. High oestrogen levels probably also contribute to spider naevi (e.g. sometimes found with high oestrogen levels during pregnancy) and possibly to the palmar erythema associated with liver dysfunction.

(d) **Failure of the liver to detoxify.**

(i) **Endogenous substances**. This particularly refers to potentially toxic substances produced by bacterial action in the large gut and normally cleared by the liver. The first of these are vasodilator amines, which may contribute to the vasodilatation of chronic liver disease, to palmar erythema and possibly to spider naevi. Ammonia also tends to accumulate, because the diseased liver cannot convert it into urea. High levels of ammonia and other toxic amines and metabolites accumulate in severe liver failure and this results in what is referred to as hepatic encephalopathy, the signs of
which include, in order, altered behaviour and sleep pattern, constructional dyspraxia, confusion, disorientation, drowsiness, asterixis (metabolic "flapping" tremor), oliguric renal failure with reduced renal blood flow, hepatic foetor, hyper-reflexia, coma, and death. Note that some of these signs of encephalopathy can be seen in the presence of relatively normal liver cell function, particularly when the pathological process is related to chronic inflammation giving rise to scarring and an altered relationship between the (regenerated) liver cells and their blood supply, and causing in effect a porto-systemic shunt of blood past the liver. This syndrome is then called porto-systemic encephalopathy (also seen with porto-systemic shunts made surgically to relieve portal hypertension).

Any tendency to hepatic encephalopathy can be reduced by purgatives (which diminish large bowel content), by antibiotics (which destroy the bowel flora) and by acidification through oral lactulose administration (which favours the growth of lacto-bacilli in the colon - the consequent lowering of pH in the gut traps ammonia there as the ammonium ion, so decreasing its absorption). As a corollary, porto-systemic encephalopathy may be precipitated by increased intestinal protein (e.g. gastro-intestinal blood, increased oral protein intake) via a consequent increase in gut ammonia production through endogenous bacterial activity.

(ii) Exogenous substances - clearance of drugs often reduced in liver failure. Particularly important are those whose enzyme clearance by the liver is normally very high, and with large reserve, so that their clearance becomes more dependent on liver blood flow than liver cell function. Such drugs normally have a high "first-pass" effect. This becomes especially important with drugs which may suppress the central nervous system, particularly in the presence of background porto-systemic shunting, where normal drug dosage may produce very high systemic plasma levels (lack of first-pass effect) and precipitate porto-systemic encephalopathy (e.g. morphine).

(e) Portal Hypertension.

This is a frequent accompaniment of hepatic scarring and in its own right leads to increased back pressure causing splenomegaly and to the opening up of connections between the portal and systemic circulations (therefore signs of caput medusa; oesophageal varices which may bleed torrentially; and rectal varices). This leads to structural and functional intra-hepatic shunts from a porto-systemic bypass. This becomes particularly important when an increased load of toxic materials is imposed from the gut, as in gastro-intestinal haemorrhage, high protein diet, constipation; or when there is an accumulation of drugs normally cleared by the liver, particularly those which act on the brain.

Arterio-venous shunting may also occur in the lung in severe liver disease, even enough to cause cyanosis - Is this the spider inside her?

(f) The origin of some of the other signs of (chronic) liver dysfunction are obscure. They include clubbing of the fingers, Dupuytren's contractures, red cell macrocytosis and "target"-shaped red cells, as well as hypogonadism in the female. Some of these signs may not be related to the chronic liver
disease per se, but to the associated alcoholism which is its most usual cause. Thus, alcoholism probably aggravates any tendency for thrombocytopenia, red cell changes, Dupuytren's contracture, and testicular atrophy; and it may be the sole cause of parotid gland swelling and perhaps also of hypogonadism in the female.

COMMENT

The classical indicator that any jaundice has an hepatic basis, anatomically, is the presence of bilirubin and increased amounts of urobilinogen in the urine. In many cases there will be further clues from evidence of impairment of hepatic function, particularly in patients with a chronic clinical picture (see also discussion on Anatomical/Pathological diagnostic overlap below).

3. POST-HEPATIC JAUNDICE

This is obstructive jaundice (or cholestasis), i.e. jaundice due to obstruction somewhere within the bile duct drainage system. Clinically, it is distinguished by severe itch from retention of bile salts. Patients also have pale "clay-coloured" and bulky stools (no bile in gut therefore no stercobilin in stool; also fat maldigestion). Bile is present in the urine, because the bile which accumulates here is water soluble conjugated bilirubin; the patient may notice that the urine is dark or olive-coloured. In the case of complete obstruction, there is no urobilinogen in the urine (no sterocobilinogen is formed in the gut). The urine may froth abnormally during micturition (due to presence of bile salts).

More generally, bruising may also occur from prothrombin deficiency, due to (fat soluble) vitamin K malabsorption because of the absence of bile salts in the intestine. However, in this case, the defect in coagulation (measured by prothrombin time) is readily corrected by the parenteral injection of vitamin K (contrast hepatic jaundice).

In long standing obstructive jaundice the liver may enlarge substantially and develop a firm edge. However, ascites and other more general signs of hepatic dysfunction do not develop. Cholesterol may also accumulate due to failure of excretion in the bile and so skin xanthomata may gradually develop. Osteomalacia may develop from vitamin D malabsorption in long-standing cholestasis. Such features are, of course, highly relevant to our Pathological diagnosis (i.e. "Chronic").

Level of Biliary Obstruction

Once we have established that our patient has obstructive jaundice, we have to take our usual hierarchic approach to determining the level of obstruction. Note in this respect that jaundice cannot arise merely from obstruction of one of the two main hepatic ducts, but it can do so from obstruction below this, mostly either due to gallstone obstruction of the common bile duct or common duct compression by pancreatic disease. In the former case, the obstruction and therefore symptoms are
usually intermittent, so that the patient characteristically notices fluctuating jaundice. Bile stasis also predisposes to secondary (bacterial) cholangitis, so there may be intermittent fever as well, (so-called Charcot's intermittent fever).

In the history any pain will, as usual, aid our localisation of the anatomical site of the problem, particularly the pain site, radiation, nature, precipitating, aggravating and relieving factors. Thus, the pain of acute pancreatitis (where swelling of the pancreatic head may occlude the intra-pancreatic course of the common bile duct) is usually a central, constant epigastric pain boring through to the back, and in some patients precipitated by alcohol abuse. On the other hand, the pain of common bile duct obstruction by stone is typically colicky in nature, tends to be felt in the right hypochondrium and classically radiates around to the back rather than through to it; in addition, if the gall bladder is inflamed from secondary ascending cholangitis and associated cholecystitis, there may be radiation to the right shoulder tip (gall bladder adjacent to the right hemidiaphragm, therefore diaphragmatic inflammatory pain referred in phrenic nerve distribution C3, 4).

Obstruction at the level of the ampulla of Vater by carcinoma may declare itself not only as obstructive jaundice, but also as blood in the stool; this blood, plus the clay-coloured appearance related to common bile duct obstruction characteristically gives the stool an aluminium colour in this (rare) condition (where both Anatomical and Pathological Diagnoses can be made from the same information).

You may also get useful information about Anatomy on examination, the abdomen being rather more accessible to the inspecting eye and the palpating hand than some other organ-systems. In this respect you should pay especially careful attention to the gall bladder. Murphy's sign is easy enough to detect (gall bladder tenderness on inspiration under the right 9th rib in the midclavicular line on inspiration), but detecting a non-inflamed distended gall bladder is more difficult because of its motility. In fact, you may more readily see it than feel it, so spend some time kneeling beside the bed looking tangentially across the abdomen for gall bladder movement. The importance of a palpable gall bladder lies in Courvoisier's law which states broadly that when the gall bladder is distended and palpable in any case of common bile duct obstruction, the obstruction is due to some cause OTHER THAN GALLSTONE. This is because gallstones, which are formed in the gall bladder, are usually associated with chronic gall bladder inflammation and this gives rise to fibrosis and hence a relatively nondistensible gall bladder. However, the reverse is not true, namely that if you find a nondistended gall bladder, the obstruction may still be due to something other than gallstone (chronic cholecystitis being so common).

Comment

Paying careful attention to the features of pain, the colour of the stool, any intermittency to the jaundice, and whether or not the gall bladder is palpable, will frequently give you the clinical diagnosis of the level of obstructive jaundice. However, in some cases symptoms and signs may be absent, (e.g. lack of pain is typical of carcinoma of the head of the pancreas causing common duct
obstruction), and then it becomes very important that we distinguish surgically-remediable causes of obstructive jaundice from 'medical' ones (i.e. widespread obstruction of the intra-hepatic bile duct canaliculi from various causes - see Aetiological Diagnosis below).

1. Difficult Cases:

1. In simple cases, all is straightforward, but in reality clinical diagnosis of the anatomical level of jaundice can be very difficult, particularly where chronic. This is because we often get a mixed picture as the process progresses in time. Thus, chronic liver disease can produce widespread intra-hepatic scarring, and this can impinge on the small bile duct canaliculi to produce an obstructive element as time goes by. Such a picture is especially apt to occur in the setting of acute (alcoholic) hepatic damage superimposed on a background of chronic cirrhosis, where previous scarring around each (abnormal) liver lobular acinar unit can limit the degree of expansion when the liver cells within it become acutely damaged and swollen, so tending to collapse the bile duct canaliculi. This is probably the reason why acute-on-chronic hepatitis sometimes presents as an apparently obstructive jaundice. The presence or absence of signs of chronic liver dysfunction (especially ascites) then become very important in diagnosis.

2. In chronic obstructive jaundice an element of ascending cholangitis can develop and produce inflammation which eventually involves the liver cell, so producing hepatic dysfunction. Also, we have already seen that obstructive jaundice due to stone may be intermittent, so that if one is "unlucky" enough to see the patient in a quiescent phase, there may be both urobilinogen and bilirubin in the urine to cause confusion.

3. If chronic obstructive jaundice is resolving, there may well be urobilurogen in the urine, as well as bilirubin.

4. In chronic haemolytic jaundice, bile pigment stones may eventually form in the gall bladder because of the high concentration there of conjugated bilirubin; and rarely, if such gallstones find their way into the common bile duct, an obstructive element may become superimposed on the chronic haemolytic jaundice process. (Again beware of diagnosing haemolytic jaundice alone in any patient who has a bilirubin more than 4-6 times elevated).

5. When the problem is difficult to localise anatomically, remember the following

Rules of thumb:

a) If the gall bladder is distended and palpable, there is an obstruction of the common bile duct not due to gall-stone.

b) If there is any ascites at all, it is extremely unlikely that the picture is purely one of obstructive jaundice.
c) Always exclude a surgically remediable cause of jaundice.

Value of investigations in further defining the anatomical site of the lesion producing jaundice

The first principle, as always, is to do non-invasive investigations first. In this respect, plasma alkaline phosphatase is particularly useful, being classically elevated to more than twice normal in obstructive jaundice (it largely comes from the bile duct canaliculi, is normally excreted in the bile and its synthesis is induced by retained bile acids), and elevated less than this in ordinary forms of hepatic disease. (In metastatic neoplasia of the liver plasma alkaline phosphatase may also be greatly raised, this time from local obstruction of bile duct canaliculi, but such patients are not usually jaundiced, because some segments of liver remain unaffected).

If bilirubin level is very high, jaundice is unlikely to be haemolytic. In addition "hepatic" enzymes, e.g. lactate dehydrogenase or LD, gamma glutamyl transferase (gamma GT) and alanine-amino transferase (ALT) are frequently raised in conditions associated with liver cell damage, especially gamma GT in obstructive jaundice. However, these enzymes are not entirely specific to the liver, and may be released in conditions of damage to other tissues and organ systems (iso-enzyme analysis helps).

Thus, these biochemical tests can give more detailed evidence on Anatomy (and Pathology) once we have localised the problem to the liver. More directly (and more invasively), 'skinny needles' passed into the liver can be used to outline the bile ducts by radio-opaque contrast material and show whether they are dilated, and the bile ducts can now also be visualised by radiological (CT) scanning, ultrasound, and by retrograde endoscopy via the mouth/ampulla of Varter (ERCP). Fine needle liver aspiration or biopsy can also be performed. One might think that the bile ducts could be outlined non-invasively by giving a radio-contrast medium intravenously. However, although this is useful in non-jaundiced patients, when any patient is jaundiced the liver cells will just not concentrate the dye sufficiently for even a high-dose cholangiogram of this type to be useful.

The above should allow a detailed diagnosis of the type and anatomical site of the lesion in any patient with jaundice. It also illustrates the principle of how you investigate only where you are unsure in any of the four diagnostic categories. In this respect, we tend to err on the side of extensive investigation of any case of jaundice, particularly those where bile duct obstruction is suspected, because we cannot afford to miss a surgically-remediable cause of obstructive jaundice. Specifically, always think of gallstone obstruction. This is our old principle of always excluding remediable causes of any condition, no matter how unlikely from the clinical presentation. (As with the kidney, you must leave no stone unturned!)

B. CLINICAL PATHOLOGICAL DIAGNOSIS
As usual, the onset, time-intensity relationships, and the presence or absence of fever and weight loss, form the backbone of our pathological diagnosis. For example, if obstructive jaundice is acutely remitting and relapsing over a period of time and of anatomically obstructive type, this suggests obstruction by stone (causing partial varying to complete obstruction). Chronic relentlessly progressive (obstructive) jaundice on the other hand, without fever, would suggest chronic pancreatitis, or if weight loss were prominent, carcinoma of the head of the pancreas.

**Fever**, as usual, suggests inflammation. This does not necessarily mean infection however, e.g. it is often seen in acute alcoholic "hepatitis", where it is probably secondary to liver cell necrosis. In cases of obstructive jaundice, any fever is often due to intermittent obstruction by stone allowing intermittent stasis and access of organisms such as E. coli to the common bile duct and therefore intermittent ascending cholangitis (Charcot's intermittent fever).

Chronic progressive weight loss, in the absence of fever, tends to suggest a neoplastic process, but chronic pancreatitis can be very indolent, and without fever. Just to make life difficult, some carcinomas may give rise to fever, particularly Ca pancreas, kidney and caecum. This can be associated with inflammation secondary to necrosis, but is sometimes due to release of so-called tumour necrosis factor (TNF).

Examination of the jaundiced patient may also yield information about Pathology, more so in the abdominal system than some others. Thus, the liver itself may be enlarged and tender in acute hepatic inflammation, though the liver edge is soft. In more chronic liver disease processes the liver edge will tend to be firm, and in neoplastic liver diseases the metastatic nodules can usually be clearly felt, giving the liver a hard 'craggy' edge and 'knobbly' surface to the palpating hand. Characteristically, an enlarged firm liver suggests disease or infiltration of the liver itself, but long-standing obstructive jaundice can also result in firm liver enlargement.

### Diagnostic Category Overlap

In discussing other organ systems and symptoms, we have noted time and again how different diagnostic categories often overlap, and do so in a way that can aid the complete diagnostic problem-solving process. In chapters so far, this has particularly related to the Functional diagnosis providing a basis for our Anatomical one, especially in relatively hidden organs like the brain. And this, as we have seen, is also true of jaundice (e.g. the functional diagnosis of ascites militates against any jaundice being anatomically of post-obstructive type). But in addition, jaundice provides an example of where there can be useful overlap between our Functional and the Pathological diagnostic categories. Thus when we see the "full house," as it were, of signs of liver cell dysfunction (e.g. spider naevi, portal hypertension, hypoalbuminaemia, ascites, oedema, palmar erythema, gynaecomastia, etc.), we can be fairly sure that the condition is, pathologically speaking, chronic. If there are signs of hypoalbuminaemia (oedema, ascites etc.) and a reduced prothrombin time (easy bruising) without these other signs of liver dysfunction, then this is consistent with the condition being...
much more acute (half-life of albumin degradation 17 days). If there is easy bruising only, in the absence of any hypoalbuminaemia, then the condition may have only been going for a matter of days (half life of factor VII only 4-6 hours).

Again, if the patient has the functional signs of portal hypertension in the presence of liver disease, it is likely that the pathological process is a diffuse chronic inflammatory scarring (narrowing and distorting the portal and hepatic drainage system) rather than one of, say, patchy hepatic infiltration.

Finally, chronic 'medical' obstructive jaundice can give rise to the secondary functional consequences of osteomalacia (Vitamin D malabsorption) as well as cholesterol deposits (xanthomata) in the skin (cholesterol not excreted, and its synthesis in the circulation is induced by retained bile salts).

C. FUNCTIONAL DIAGNOSIS

Discussed above because of its importance to localizing the anatomical site of the lesion, as well, in this case, as helping to define the nature of the clinical pathological process involved. But the Functional diagnosis is also important in its own right, especially in treatment e.g. IV vitamin K1 for bruising due to vitamin K malabsorption from bile salt deficiency in obstructive jaundice.

Whilst discussing functional diagnosis, we should always think of cause and effect, e.g. whether we are dealing with primary liver disease and secondary hepatomegaly ascites, oedema etc., or whether the hepatic dysfunction etc. is secondary to some other primary problem. Thus, severe chronic right heart failure can give rise to secondary hepatic enlargement and dysfunction associated with chronically elevated hepatic back pressure on the liver cells, with secondary ascites, jaundice, elevated enzymes, and even sometimes fibrosis with alteration in liver cell architecture (particularly in chronic tricuspid valve incompetence). This illustrates the importance of a complete and accurate examination of all systems in your patients, and not just of the obvious system which strikes you as abnormal.

Finally, bear in mind the importance of Occam's razor in diagnosis i.e. making a minimal primary diagnosis which can explain all the signs - which in liver disease are often so manifold that you can readily be trapped into thinking you are dealing with a multi-system disease unless careful.

D. AETIOLOGICAL DIAGNOSIS

There are many causes of haemolytic jaundice, perhaps the most important being congenital spherocytic haemolytic anaemia; also acquired auto-immune haemolytic anaemia where for some peculiar reason, the body develops antibodies against its own red cells. Intravascular haemolysis can
also occur in conditions where there is vascular disease particularly in the presence of severe vascular narrowing and/or endothelial damage, as in small vessel "vasculitis" and severe hypertension (roughened narrow roads soon wear red cells out); also with artificial heart valves etc. which cause direct traumatic red cell haemolysis. Drugs can also cause haemolytic anaemia (e.g. methyldopa). Abnormal red cells may be more prone to haemolysis as well, e.g. the macrocytes of vitamin B12 deficiency. Most of the more usual forms of haemolysis occur in the spleen as we might expect, and this can be related either to a primary red cell defect of some sort as above, or secondary to an enlarged spleen (so-called hyper-splenism).

The commonest aetiologial factor underlying liver disease as a cause of jaundice in our community is chronic alcoholism with or without super-imposed bouts of acute alcoholic "hepatitis" during "binges". Other important causes are viral hepatitis including hepatitis A, B and C, of which the latter two, particularly hep. C, can subtly progress to become chronic. In addition there are other (non-viral) active progressive forms of liver disease which have an auto-immune basis. In these days of increasingly efficacious drugs, drug-induced liver disease from side-effects is becoming an increasing problem; such drugs include non-steroidals, halothane, and amiodarone. Some of these act through a direct toxic effect, yet others by an allergic reaction and others still by an idiosyncratic response on the part of individual patients.

Obstructive jaundice due to gallstone is usually related to cholesterol gallstones, but remember pigment gallstone obstruction in patients with chronic haemolytic anaemia. Chronic pancreatitis obstructing the common duct often arises in the setting of chronic alcoholism, but may be idiopathic. Carcinoma of the pancreas is predisposed to by heavy cigarette smoking.

So far we have only mentioned 'medical' causes of obstructive jaundice in passing. Medical obstructive jaundice includes cases where the pathological process involves not so much the hepatic parenchymal cell, but the bile duct canaliculi which swell and cause obstruction at that level rather than at the more surgically-approachable level of the common bile duct. We often refer to this as "intrahepatic cholestasis", and it has a number of causes, particularly drugs such as phenothiazines (where the mechanism is thought to be immunological), and methyltestosterone/anabolic steroids (where it seems more a toxic reaction). Some forms of viral hepatitis may also go through a cholestatic phase.

Bile duct obstruction can also be the result of a process of scarring of the common bile duct, as in the autoimmune disease 'primary sclerosing cholangitis' similar scarring is also sometimes also seen in patients with ulcerative colitis.

**MCQs & PROBLEM SOLVING**

**Mechanisms in Disease**
A patient is sent to your ward with a diagnosis of jaundice secondary to chronic liver disease.

Which of the following would be characteristic features.

1. Severe itch.
2. Colicky right-sided sub-costal abdominal pain radiating around to the back.
3. Easy bruising correctible by the injection of vitamin K parenterally for two days.
4. Absence of urobilinogen from the urine.
5. The presence of bilirubin in the urine.
6. Evidence of osteomalacia from vitamin D malabsorption.
7. Palmar erythema.
8. Gynaecomastia.
9. Testicular atrophy.
10. The presence of spider naevi over the upper trunk, face and arms.
11. Finger clubbing.
12. Red cell macrocytosis and target cells on the peripheral blood film.
13. Elevation of plasma alanine-amino transferase (ALT) and gamma GT.
14. Hepatitis C infection as a cause.

Answers at end of chapter.

Problem Solving
A 57 year old (1) housewife (2) presents with a six year history (3) of recurrent right upper quadrant abdominal pain radiating round to the back (4), occurring every 2-3 months on average (5) and lasting anything from a few hours to several days (6). The only identifiable precipitating factor has been unduly fatty meals (7). Each attack comes on fairly abruptly (8) and the pain is sometimes of very "colicky" or "griping" (9) nature, often quite severe, when it is associated with sweating and vomiting (10) and is relieved to some extent by the local application of a hot water bottle over the right hypochondrium (11). In more severe and prolonged bouts there is often tenderness under the right costal margin (12) and pain radiating to the right shoulder tip (13). Such attacks are sometimes associated with fever (14).

In the past two months she has had more frequent pain (15), and in addition, noticeable jaundice (16), she thinks perhaps somewhat variable (17), as well as intermittent shivers and sweats (18). In the last week the jaundice has deepened (19), and she has developed an itch (20), easy bruising (21) and pale bulky stools (22). The urine has also become dark (23) and she has noticed a great deal of urine frothing in the toilet bowl whilst it is being flushed after micturition (24). There is a family history of myocardial ischaemia, and because of this, the patient had a "blood check" ten years ago, after which she was told to lose weight and take a "low-cholesterol" diet (25). Medications: methyldopa 250 mg bd (26) for mild hypertension, for the past 12 months. She admits to only "occasional" alcohol intake (27). Non-smoker (28).

Examination during a current attack reveals a somewhat obese woman (29) with multiple superficial skin bruising (30), scratch marks (31), and moderate jaundice (32). Hands normal (33). Not clinically anaemic (34). Temp. 37.4 deg. C (35). Blood pressure 150/90 mm Hg (36), JVP normal (37), CVS otherwise NAD. No oedema (38). Chest NAD. Abdomen - 4 cm of smooth slightly tender liver palpable below the costal margin (total liver span 16 cm with a regular smooth lower edge) (39). Also, an indefinite rounded mobile non-tender mass felt in the right upper abdomen, the size of a small orange, which moves downwards on inspiration, is felt best as the patient's abdominal muscles relax early during expiration, is ballottable from the loin, and resonant to percussion anteriorly (40). No splenomegaly, and no ascites (41). Urine examination shows bile but no urobilinogen (42). Rectal examination reveals soft pale yellow stools (43), negative for blood testing (44).

Now solve the problem in the usual way, using your usual four column approach, and then answer the following questions.

Solving the Problem. Now draw up your usual four columns (widest for "How?" column), and work through to a solution of this problem linking inferences leading to like conclusions. Then make a final overall diagnosis before answering the MCQs below.

Graphic Solution: Available in next section as a jpeg. When viewing, centre the picture so that all 4 columns are able to be seen at the same time. The solution is available in two parts.
Diagnostic Dissertation. Think of what investigations you wish to see in this patient before viewing the solution.

MCQs. Also, consider the following questions about the case before turning to the graphic solution. MCQ answers available in the final section of this chapter.

Which of the following is/are likely to be correct?

1. The pain described over the years is characteristic of (relapsing) pancreatitis.

2. The pain radiating to the shoulder in severe episodes suggests inflammation involving the anterior abdominal wall.

3. The shoulder tip dermatome is approx. C6.

4. The skin itch is most likely related to retention of bile salts.

5. The easy bruising would characteristically be correctible by parenteral vitamin K in this patient.

6. The episodic fever may well be related to intermittent ascending cholangitis.

7. The rounded mass in the right upper abdomen is probably a distended, palpable gall bladder.

8. In view of the fatty stool, we would expect this patient to have an abnormal xylose tolerance test.

9. The absence of ascites is a surprising finding.

10. Characteristically we would expect to find evidence of osteomalacia in this patient.

11. This is a classical picture of pre-hepatic (haemolytic) jaundice.

12. Characteristically, we would expect to find plasma levels of alkaline phosphatase elevated to more than twice normal.

13. The increased urine frothing is probably related to occult proteinuria.

14. She may well have had hypercholesterolaemia for some years, relevant to her condition.

15. Carcinoma is likely as the basic cause of this patient's condition.

16. Methyldopa is not likely to be relevant to the jaundice in this patient.
17. Aetiologically, alcohol is a real possibility as the underlying causative agent.
Ch. 13. Jaundice Problem.

|--------|-------|------|------|

Interim Conclusion. — as usual, when time-intensity relationships are about to change.


Further Progress. — More severe attacks.


Interim Conclusion. — Recent severe attacks.

2. Gall bladder & Peri-Gall Bladder ⇔ Inflammation \[ \equiv \] Peri-gall bladder/diaphragmatic involvement with 2 colic & shoulder tip pain. Prolonged Obstruction to cystic duct \[ \equiv \] Stasis

A further change in time-intensity Relationships. Therefore, time to rule off and start a New Series of Columns.

| 15. Two months more frequent pain = recent↑ in episode frequency | 15. More frequent pain recently. ? Any different than before, particularly in 16. 16. Variable jaundice |
| 18. Intermittent shivers & sweats. = episod. inflammation |
Another change has just occurred in time-intensity relationships. Therefore, rule off again and draw Further Interim Conclusions before proceeding.

Ch. 13. (contd.)  Jaundice Problem.

| Episodic stasis .

Taken together with previous biliary colic, the occurrence of jaundice now raises the question of Possible obstruction of the common bile duct (CBD). Jaundice is variable, therefore => CBD obstructn. variable . <= (But need more evide. of CBD. obstrn.)

Why changed? —the site of obstruction has prob. shifted from cystic duct to CBD, ? due to = Shift of a stone.

Further history.


19. (Recent) deepening jaundice
20. Itch = bile salt retention
22. Pale bulky stools = ? steatorrhea

↓

19.-22. = ? CBD obstruction.

25. HH. of myocardia.
26. Meth dopa occas. causes haemol., haemagl. jaund., but not 'obstructive' 27. 'Occas. EtoH'.
28. Cigs. — nil.

Further Interim Conclusion.

CBD. Acute Obstruction. Cholesterol Stone

Examination Findings.

29. Obese.
32. Mod. jaundice.
30-32. All compatible with => Stasis = CBD obstruction.
33. Hands normal.
34. No cln. anaemia.
36. BP. borderline.
37. JVP. normal.
38. No oedema.

29. ? predisposed to stone.

= No evid. of generalised inflamn. ↓
39. Liver non-tender — surprising in view of pain etc. Inflammation must be settling

39. Liver mod. enlarged . ? 2" to bile duct obstruction
40. This is a high post. abdo. mass, prob. kidney , but certainly no palpable gall bladder . (not expected in GB, stone disease. because of Courvoisier's law )
41. No enlarged spleen, no ascites = no evid. of (2") liver disease
42. Urine contains bile but no urobilinogen , consistent with Complete bile duct obstruction.
43. Pale faeces — ? steatorrhea from CBD. obstruction.

Has the patient had antibiotics recently? *Ask relatives.
PROBLEM SOLUTION-3

<table>
<thead>
<tr>
<th>Final Interim conclusion.</th>
<th>Jaundice (contd.)</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where?</td>
<td>What?</td>
<td>How?</td>
</tr>
</tbody>
</table>
| 4. CBD. | Obstruction with 2" stasis | 2° bile salt defic.  
→ maldigestion  
→ fat malabsorption  
→ fat soluble vit. (K) defic. | Cholesterol stone in cystic duct  
→ shift to CBD. |
| Acute inflamn./infection above point of obstruction  
(Setting ) | | ? Recent antibiotics. |

Conclusions.

<table>
<thead>
<tr>
<th>Anatomic Diagnosis.</th>
<th>Pathological Diagnosis.</th>
<th>Functional Diagnosis.</th>
<th>Aetiol. Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| 2. Gall bladder      | More severe bouts — prolonged obstruction  
↓ Stasis.  
↓ Inflammation | Severe biliary colic.  
← local tenderness/pain  
+ shoulder tip pain from diaphragmatic involvement | Cholesterol stone in cystic duct. |
| + Peri-gall bladder. |                       |                       | |
| 3. Common Bile Duct | Acute, more severe episodic obstruction.  
↓ 2" stasis  
↓ Inflammation. | Intermittent obstructive jaundice.  
← Cholesterol stone now loose in CBD. |
| ↓ Dilatation of ducts & ductules above |                       |                       | |
| 4. CBD. ▸ | Obstruction with 2" stasis  
↓ Acute inflammation/infection above point of obstruction  
— now settling. | 2° bile salt defic.  
→ maldigestion  
→ fat malabsorption  
→ fat soluble vit. defic. | Cholesterol stone in cystic duct  
→ shift to CBD. |
| | | | ? Recent antibiotics. |
PROBLEM SOLUTION-4

Ch. 13 Jaundice (cont’d.)

Diagnostic Dissertation/Comment.

Points.

A. USEFUL INVESTIGATIONS.

1. Functional diagnosis.
   b). Reduction of prothombin time. — &,
   if so, is it reversible with I.V. vit K? (as we would expect in obstructive jaundice).

2. Pathological diagnosis.
   a). Full blood examination - ? increased neutrophil count secondary to infection
   b). ? any spread of inflammation/infection, particularly to blood.
   — blood cultures.

3. Anatomical diagnosis.
   a). Abdominal ultrasound to confirm presence of gallstones in GB/CBD.
   May need ERCP.

4. Actiological Diagnosis.

B. TREATMENT.

1. Functional
   a). Pain relief.
   b). Treatment to relieve itch.
   c). IV. Vit K — to correct prothombin deficiency.

2. Pathological.
   a). Appropriate antibiotics: partic. if any bacteraemia/septicaemia.
   b). Local: to alleviate abdo. inflammatory pain.

3. Anatomical.
   a). Remove GB. & CBD. stones as soon as possible, under antibiotic cover:
   ideally operate only after any inflammation has settled with antibiotics,
   — but provided patients condition is improving!
   Hence value of the alternative ERCP.

   a). Take steps to lower plasma cholesterol, if elevated.
   This will not only help prevent recurrence of gall stones, but, also
   help prevent future atherosclerotic arterial disease.
MCQ ANSWERS

MCQ Answers

1. Mechanisms in Disease
5, 7, 8, 9, 10, 11, 12, 13, 14 correct. All others false.
Q 6: Osteomalacia from any vitamin D malabsorption in primary liver disease is rare.

2. Problem Solving MCQs
4, 5, 6, 12, 14 16 correct. All others false.

Explanations:
Q 7. relates to obs. 40. The description is of a posterior mass: ballottable from the loin, and dull to percussion anteriorly, and probably the R. kidney. Don't just idly assume that this is the gall bladder (an anterior mass) merely because the case is about jaundice!
Q 8 is false. Xylose absorption is diminished in patients with decreased intestinal mucosal function, as in coeliac disease.
Q 10: Whilst it is true that (fat soluble) vitamin D absorption will be reduced, in this patient the condition has not be present for long enough to result in osteomalacia.