Primary Sclerosing Cholangitis (PSC)

Introduction

Primary sclerosing cholangitis (PSC) is an uncommon condition affecting the bile ducts and liver. Inflammation and scarring of the bile ducts can lead to liver damage and cirrhosis - a condition where normal liver tissue is replaced by scar tissue (fibrosis). It is called:

- **Primary** - because the cause is not known. (That is, it is not 'secondary' to any known cause such as alcohol or poisons.)
- **Sclerosing** - because it causes scarring and thickening (sclerosis) of the bile ducts.
- **Cholangitis** - which means inflammation of the bile ducts.

Different treatments are available to control symptoms that may develop and also to manage any complications which may occur. The outlook for people with primary sclerosing cholangitis can be very variable.

What is Primary Sclerosing Cholangitis?

The liver is in the upper right part of the abdomen. It has many functions which include:

- Storing glycogen (fuel for the body), which is made from sugars. When required, glycogen is broken down into glucose which is released into the bloodstream.
- Helping to process fats and proteins from digested food.
- Making proteins that are essential for blood to clot (clotting factors).
- Processing many medicines which you may take.
- Helping to remove or process alcohol, poisons and toxins from the body.
- Making bile, which passes from the liver to the gut down the bile duct. Bile breaks down the fats in food so that they can be absorbed from the bowel.
Bile ducts are tubes which carry bile (a greenish yellow liquid made by the liver) into the upper part of the bowel. Bile acts as a detergent breaking up fat from the food we eat into small droplets that can then be absorbed into the body. It also enables the body to absorb vitamins A, D, E and K from our diet.

Bile is made by liver cells. Liver cells pass out bile into tiny tubes called bile ducts. There is a network of bile ducts in the liver. They join together (like branches of a tree) to form the larger 'common bile duct'. Bile constantly drips down the tiny bile ducts, into the common bile duct, and into the duodenum (part of the gut - the first part of the small intestine).

The gallbladder lies under the liver. It is like a pouch off the common bile duct and fills with bile. It is like a reservoir that stores bile. The gallbladder squeezes (contracts) when we eat. This empties the stored bile back into the common bile duct and out into the duodenum.

In this condition, the bile ducts both inside and outside the liver become inflamed and scarred. The scarring causes narrowing of these bile ducts which results in bile building up in the liver. The bile can then damage the liver cells. Eventually, the scar tissue can spread throughout the liver, causing cirrhosis and liver failure. Cirrhosis is a serious condition where normal liver tissue is replaced by scar tissue (fibrosis). It tends to progress slowly and often does not cause symptoms in its early stages. However, as the function of the liver gradually becomes worse, serious problems can develop.
What are the symptoms of primary sclerosing cholangitis?

Many people have no symptoms at first and the disease is only discovered because of abnormal results of routine blood tests in patients with ulcerative colitis or Crohn’s disease. In some people PSC does not produce any symptoms. Most people have few or no symptoms for many years.

Common early symptoms are:
- Tiredness
- Some abdominal discomfort in the right upper abdomen.

Late symptoms are:
- Itching
- Jaundice
- Episodes of fever, shaking and chills can be distressing but are uncommon.
- Liver failure may ultimately develop.

PSC may be occasionally complicated by the development of bile duct cancer.

Jaundice is when you 'go yellow'. You tend to notice it first when the whites of the eyes become yellow. This is due to a build-up of the chemical bilirubin, which is made in the liver and, in some liver conditions, spills into the blood.

Cause, Prevention and Related Diseases

It is not possible to prevent PSC because the cause remains unknown. Liver damage and cirrhosis is often presumed to be caused by drinking too much alcohol, however PSC is not related to alcohol in any way.

Current evidence suggests that the disease may be triggered by an unknown bacteria or virus in people who are genetically programmed to get the disease. The common viruses known to cause hepatitis have not been associated with it.

PSC has a significant association with ulcerative colitis, an inflammatory bowel disease primarily affecting the large intestine. As many as 5% of patients with ulcerative colitis may progress to develop primary sclerosing cholangitis and approximately 70% of people with primary sclerosing cholangitis have ulcerative colitis.

The frequent occurrence of PSC in association with inflammatory bowel disease suggests that a common cause for both diseases may exist or that the inflamed colon allows toxins or infections to be absorbed into the body and this can cause the bile duct inflammation.

Disease Staging

Ludwig and associates described 4 stages of PSC, as follows:

Stage 1: Portal hepatitis, degeneration of bile ducts with inflammatory cell infiltrate
Stage 2: Extension of disease to periportal area with prominent bile ductopenia
Stage 3: Septal fibrosis and necrosis
Stage 4: Frank cirrhosis
What are the complications of primary sclerosing cholangitis?

Various complications can occur in some people with PSC. These include:

Deficiencies of some vitamins, usually vitamins A, D, E and K. These are the vitamins which are fat-soluble (rather than the other vitamins which are water-soluble). This means they dissolve in fat. Bile helps the fat to be broken down and these vitamins to be absorbed.

Osteoporosis - People with primary sclerosing cholangitis may experience thinning bones. Your doctor may recommend a bone density exam to test for osteoporosis every few years. Calcium and vitamin D supplements may be prescribed to help prevent bone loss.

Cholangitis - The narrowing of the bile ducts predisposes the bile to bacterial infection (cholangitis). Cholangitis is a serious and potentially life-threatening infection with fever, shaking chills (rigors), jaundice, and upper abdominal pain. Cholangitis can result in bacterial infection spreading to the bloodstream (a condition called sepsis). Sepsis can cause damage to kidneys and lungs and even cause shock.

Portal hypertension - Your portal vein is the major route for blood flowing from your digestive system into your liver. Portal hypertension refers to high blood pressure in this vein. Portal hypertension can cause fluid from the liver to leak into your abdominal cavity (ascites). It can also divert blood from the portal vein to other veins, causing these veins to become swollen (varices). Varices are weak veins and tend to bleed easily, which can be life-threatening.

Cholangiocarcinoma (cancer of the bile ducts) is more common among patients with primary sclerosing cholangitis. An estimated 9%-15% of patients with primary sclerosing cholangitis will develop cholangiocarcinoma, a very lethal type of cancer. Patients at highest risks for developing cholangiocarcinoma are primary sclerosing cholangitis patients with cirrhosis who also have long-standing ulcerative colitis.

Primary sclerosing cholangitis causes gall stones and is a risk factor for gall bladder cancer.

Long-standing chronic ulcerative colitis alone is a risk factor for colon cancer. Patients with both primary sclerosing cholangitis and ulcerative colitis have an even higher risk for developing colon cancer than patients with ulcerative colitis alone.

Liver disease and failure - As primary sclerosing cholangitis progresses, the disease causes cirrhosis of the liver (irreversible scarring of the liver) and liver failure; leading to the consideration of liver transplantation. Primary sclerosing cholangitis is, in fact, one of the more common reasons for liver transplantation. Patients with advanced cirrhosis may develop frequent infections, fluid in the ankles and the abdomen (ascites), internal bleeding from rupture of esophageal varices, and mental confusion with progression to coma (hepatic encephalopathy).
How is primary sclerosing cholangitis diagnosed?

Many people with PSC have no, or only vague, symptoms for quite some time in the early stages of the disease. Therefore, the diagnosis is often made when you have tests for an unrelated condition or routine tests if you have inflammatory bowel disease. Tests usually include:

- Liver function tests - These measure the activity of chemicals (enzymes) and other substances made in the liver. This gives a general guide as to whether the liver is inflamed, and how well it is working.
- Other blood tests may be performed to rule out (exclude) other causes of liver conditions such as viral hepatitis.
- Ultrasound scan - Often the bile ducts are examined by ultrasound to exclude the possibility of other diseases. Ultrasound is a quick examination and completely painless.
- Cholangiography - There are two main methods of obtaining a picture of the biliary tree. Traditionally, an endoscopic cholangiogram (ERCP) is carried out. Under sedation a thin tube (endoscope) containing a small camera is passed through the mouth into the small bowel (the duodenum) via the stomach. A tiny tube is then passed through the endoscope into the bile ducts, dye (contrast media) is injected and X-rays are taken to produce a picture of the bile ducts.
- A newer method is a tubeless test called magnetic resonance cholangiogram (MRCP) although the picture quality is not quite as good as ERCP. This means lying in a scanner which can be a little claustrophobic for some people.
- Taking a small sample (biopsy) of the liver. This may be carried out to look at the sample under the microscope. It can show inflammation and the extent of any cirrhosis (where normal liver tissue is replaced by scar tissue (fibrosis) in the liver). The liver biopsy can also assess how early or advanced the disease is.

What is the treatment for primary sclerosing cholangitis?

Researchers continue looking for treatments to slow or reverse bile duct damage caused by primary sclerosing cholangitis. Treatments for primary sclerosing cholangitis focus on reducing signs and symptoms of the disease as it progresses. Primary sclerosing cholangitis progresses slowly, but it usually ends in liver failure and the need for a liver transplant. Many medications have been studied in people with primary sclerosing cholangitis, but so far none has been proved to slow or reverse the liver damage associated with this disease. But until a treatment is found, doctors care for people with primary sclerosing cholangitis by reducing signs and symptoms of complications.

Therapy is aimed at treating symptoms and managing complications. Immunosuppressants, chelators, and steroids are used in an attempt to control the disease process but have not shown significant benefit. Liver transplantation is the only therapy that can alter the eventual outcome. PSC is the fourth leading indication for liver transplantation in adults.

At present there is no known cure or specific treatment for PSC although preliminary trials have suggested that the natural bile acid, ursodeoxycholic acid, may slow the progression of the disease possibly by increasing bile flow and reducing liver inflammation. Symptoms such as itching can be treated with agents such as cholestyramine, rifampicin or naltrexone.

Cholestyramine may be prescribed to help relieve itching. It works better when taken before and after meals, especially breakfast, but it may take some days before the treatment is effective. Some people taking Cholestyramine experience side effects such as altered bowel habits or bloating. If this is a problem, tell your doctor as there are other treatments such as albumin dialysis that may suit you better.
Antibiotics will be given if you have an episode of infective cholangitis.

Blockages that occur in your bile ducts can be treated with:

- Balloon dilation and stent placement. These procedures can open blockages in the larger bile ducts. Balloon dilation is a procedure in which your doctor runs a slender tube with an inflatable balloon at its tip (balloon catheter) through an endoscope and into a blocked bile duct. Once the balloon catheter is in place, the balloon is inflated. Small plastic tubes called stents may be placed in bile ducts to keep them open.
- Bile duct surgery. In certain situations, blockages in bile ducts may need to be removed surgically. After removing a blockage, the surgeon connects the remaining portions of bile duct so that bile can still flow through the duct.

Many people suffer with a dry mouth and dry eyes, but this can be helped by taking lozenges and artificial tears prescribed by your doctor.

People with advanced PSC are often deficient in vitamins A, D and K and replacement fat-soluble vitamins are given.

For a few people who eventually go on to get advanced cirrhosis, a liver transplant may be recommended when their quality of life has deteriorated and medical treatment can no longer control their symptoms. Because PSC usually develops slowly, transplantation can generally be carefully planned well ahead. Outlook following a liver transplant is good. However, PSC recurs in around a third of cases following a liver transplant.

**Prognosis**

The course of PSC is variable. If you have no symptoms then your outlook is better compared to those who develop symptoms.

Using different population study models, researchers in the Netherlands concluded that life expectancy may be longer than 21 years from the time when the diagnosis is made.

The estimated the average survival time from time of diagnosis to be approximately 25 years, and the median time until either death or liver transplantation to be approximately 10-12 years.

The prognosis and life expectancy is poorer in older patients, those who have an enlarged liver and spleen, and in patients who are persistently jaundiced with elevated bilirubin levels in their bloodstream.

Liver transplantation is the only treatment modality that appears to change the prognosis. The five year survival rate for patients who undergo liver transplantation is 85%. Liver transplantation is successful in 80 to 90 percent of adult patients.

The risk for cholangiocarcinoma is increased significantly in patients with PSC. Cholangiocarcinoma reportedly occurs in association with PSC in 6-30% of patients; on autopsy, it is found in up to 30-40% of patients with PSC.

Dominant biliary strictures can be identified in about 20% of patients with PSC and must be differentiated from cholangiocarcinoma. Strictures cause cholestasis with jaundice and pruritus and may also result in cholangitis.
Etiology and Pathophysiology

The etiology of this disease remains unknown, but a variety of factors are thought to be involved. The etiology is thought to be multifactorial, including genetic predisposition, exposure to an environmental antigen, and subsequent aberrant immunologic response to that stimulus. There is also an increased prevalence of HLA alleles A1, B8, and DR3 in PSC.

An autoimmune mechanism is suggested because approximately 75-90% of patients with primary sclerosing cholangitis (PSC) have inflammatory bowel disease (IBD). However, only approximately 4% of patients with IBD have or develop PSC. A marked increase in serum autoantibody levels occurs in patients with PSC as well, with antineutrophil cytoplasmic antibodies (ANCA) in 87%, anticardiolipin (aCL) antibodies in 66%, and antinuclear antibodies (ANA) in 53%.

In biliary ducts, an inflammatory response to chronic or recurrent bacterial infection in the portal circulation and from exposure to toxic bile acids has been postulated.[4] A genetic predisposition has been suggested because of an increased prevalence of HLA-B8, HLA-DR3, and HLA-Drw52a. Recently, genome-wide association studies performed in PSC have identified a number of genetic susceptibility loci. Subclassification of PSC patients according to their genetic predisposition may well constitute a valuable tool for future research in the subject.[5]

Ischemic damage to the biliary tree has also been postulated, since surgical trauma to the biliary tract can cause similar damage and because of the high number of patients with PSC who are ANCA–positive as observed in other vasculitides. Therefore, the most plausible concept of the pathogenesis of PSC involves the exposure of genetically predisposed individuals to an environmental antigen that subsequently elicits an aberrant immune response, leading to development of the disease.

Epidemiology

There is relatively little data on the prevalence and incidence of primary sclerosing cholangitis, with studies in different countries showing annual incidence of 0.068–1.3 per 100,000 people and prevalence 0.22–8.5 per 100,000; given that PSC is closely linked with ulcerative colitis, it is likely that the risk is higher in populations where UC is more common.

In the United States, the prevalence of primary sclerosing cholangitis (PSC) is not known. Inferences have been drawn on the basis of the strong relationship with inflammatory bowel disease (IBD). Prevalence is estimated to be 6.3 cases per 100,000 population. Western Europe is thought to have approximately the same prevalence as in the United States, though Scandinavian countries report a somewhat higher rate. In many developing countries with limited access to advanced health care, the prevalence of PSC is probably underestimated, since the diagnosis cannot be confirmed without ERCP.

It affects around 1 in 16,000 people in the UK. It can occur at any age, but is more common in people aged around 40 years.

The association of PSC with IBD may vary; for instance, in Japan, only 23% of patients with PSC have IBD. The disease normally starts at age 20-30 years, although it may begin in childhood. The disease may be active for a long time before it is noticed or diagnosed.

There is a 2:1 male-to-female predilection of primary sclerosing cholangitis. Approximately 70% of patients with PSC are men, with a mean age of diagnosis around 40 years. Patients with PSC but without IBD are more likely to be women and to be older at diagnosis.
Lifestyle Advice

Many people with PSC can eat a normal diet, while others may need more detailed advice. If you are well with few symptoms you may not need to make any changes, although it is important to eat as healthily as possible.

Many people with PSC find that they can no longer tolerate alcohol. Some may be advised to drink only a little on special occasions while others should not drink at all. Sensible drinking advice varies from person to person and will depend on many factors, such as the severity and stage of the disease, as well as your general health.

If you have cirrhosis or other complications such as fluid retention (ascites and oedema) or mental slowness or confusion (encephalopathy), you may need specialist advice.

A few people have problems digesting fat and can develop a type of diarrhoea called steatorrhoea, in which stools are bulky, pale and difficult to flush away. There may also be nausea. If this occurs, it may help to reduce the amount of fat in the diet under the supervision of a dietician. A low fat diet should be followed only if steatorrhoea is causing problems.

The aim of a low fat diet is to improve the diarrhoea, abdominal pain and discomfort associated with steatorrhoea. As fat is an important source of energy, anyone following a low fat diet should eat extra carbohydrate, such as starch and sugar.

Some people may need energy supplements and injections of fat-soluble vitamins. Others are prescribed medium chain triglycerides (MCT) which are fats that are easier to digest.

A few people experience heartburn and an unpleasant taste in the mouth, usually caused by acid from the stomach going back up into the gullet. Eating small amounts often helps. A good idea is always to carry something to eat, preferably food which contains carbohydrate.

Tiredness is the commonest symptom of PSC. Some people may need to consider making changes to their lifestyle, such as giving up work or a particular activity. Some people find that pacing their daily activities helps to preserve stamina and energy. Gentle exercise such as walking and swimming can be beneficial.

It is important to tell your dentist that you have PSC as there may be an increased risk of bleeding.

Also, there are a few medicines that are best avoided, and the dose of others may need to be reduced. For example, it is better to take paracetamol rather than aspirin to combat aches and pains. However, you should check this with your doctor first; they are best equipped to advise you.

If you are female and middle aged, it is important to discuss with your doctor the best way of reducing your risk of developing osteoporosis.

Your doctor may advise various measures which might include increasing the intake of calcium in your diet, taking calcium supplements and HRT (hormone replacement therapy) if appropriate.

Most doctors will also advise not smoking.
Other PSCer’s!

**Chris Ledoux (2 October 1948 – 9 March 2005)**
Background: American country music singer-songwriter, bronze sculptor and rodeo champion 1971-2005
Diagnosed with PSC August 2000 aged 52
Transplant October 2000 aged 52
Diagnosed with cholangiocarcinoma: November 2004 aged 56
Died Aged 56


**Michael Jerome Gillis (1949 – April 7, 2007)** was an American academic and writer.
Mr. Gillis died April 7 at Stanford University Medical Center after a 10-month battle with a rare liver disease called primary sclerosing cholangitis
Died Aged 58


**Walter Payton (25 July 1954 – 1 November 1999)**
Background: American football running back who played for the Chicago Bears 1975-1987
Diagnosed with PSC February 1999 aged 44
Death from cholangiocarcinoma in November 1999 aged 45
Died Aged 45


**James Redford (b. 5 May 1962)**
Background: Son of Robert Redford
Diagnosed with UC in 1980 aged 15
Diagnosed with PSC in 1987 aged 25
Received two liver transplants months apart in 1993 aged 31


**Karl-Gustav Fredrik Olausson (b. 5 October 1966)** is a Swedish former ice hockey player from Nybro.
Unfortunately, it was reported on February 27, 2007 that Olausson would have to retire due to serious illness (primary sclerosing cholangitis). In December 2006, he reportedly underwent two surgeries and received a liver transplant in the summer of 2007.
Transplant 2007 aged 40


**Brett Wheeler (b. 21 November 1971)** is a former professional basketball player in the NBL.
In 2009 it was revealed he suffers from PSC

Chris Klug (b. 18 November 1972)
Background: Professional alpine snowboarder.
Diagnosed with PSC 1991 aged 19
Transplant 28 July 2000 aged 27

http://en.wikipedia.org/wiki/Chris_Klug
http://chrisklugfoundation.org/

Jahine Amid Arnold (b. 19 June 1973) is a former National Football League wide receiver.
Diagnosed with PSC August 2007 aged 34

http://en.wikipedia.org/wiki/Jahine_Arnold

Myles Kane (b. 1979) is an American film producer and wizard rock artist (performing under the name MC Kreacher).
Diagnosed with PSC 2006 aged 27
Transplant 2013 aged 34

http://en.wikipedia.org/wiki/Myles_Kane

Elena Sergeevna Baltacha (14 August 1983 - 4 May 2014)
Background: Former British professional tennis player of Ukrainian background
Diagnosed with PSC 2002 aged 19
Diagnosed with Liver Cancer January 2014 aged 30
Died aged 30

http://en.wikipedia.org/wiki/Elena_Baltacha

Ben Thomas McDermott (b. 1983) - Blogger
Diagnosed with IBD 2001 aged 18
Diagnosed with PSC 2005 aged 22
Transplant May 2012 aged 29

http://mypscstory-ben.moonfruit.com/#/latest/4539784919
News:

22 April 2014 - Orbsen Therapeutics to take part in €6m liver disease clinical trial - Orbsen Therapeutics, a spin-out from NUI Galway’s Regenerative Medicine Institute (Remedi) has announced plans to partner with the University of Birmingham in a €6 million project to fight liver disease.


4 May 2014 - Commentary: A Message for ‘Generation Invincible’ - I was once a member of Generation Invincible, an overly confident 20-something who thought health insurance was something for “old people.” After all, I did everything properly. I ate healthful foods and exercised regularly.


5 May 2014 - Former British number one tennis champion Elena Baltacha dies aged 30 just two months after revealing liver cancer diagnosis - Tennis player Elena Baltacha has died less than two months after revealing she had been diagnosed with liver cancer. The former British number one had vowed to fight the disease 'with everything I have' after breaking news of her illness in March.


5 May 2014 - 'Beautiful, talented & determined' Former tennis star Elena Baltacha dies aged 30 - The Ukraine-born star lost her battle against liver cancer, aged 30.

http://www.express.co.uk/news/uk/474064/Former-tennis-star-Elena-Baltacha-dies-aged-30-following-cancer-battle

5 May 2014 - Elena Baltacha: What do we know about liver cancer? - The champion athlete learned she had the illness in mid-January, having been diagnosed years earlier at 19 with the chronic liver condition, primary sclerosing cholangitis.

http://www.bbc.co.uk/news/uk-27280436

9 May 2014 - Lumena Pharmaceuticals Now Dosing Patients in the INDIGO Phase 2 Clinical Trial of LUM001 in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis - Lumena Pharmaceuticals (Lumena), a biopharmaceutical company focused on the development and commercialization of novel products for rare cholestatic liver diseases and serious metabolic disorders, today announced the dosing of the first patient in the INDIGO Phase 2 clinical trial of its lead drug candidate, LUM001, in children with progressive familial intrahepatic cholestasis (PFIC). Additionally, the CAMEO Phase 2 clinical trial of LUM001 in adults with primary sclerosing cholangitis (PSC) is open for enrollment.

11 May 2014 - Gift of life - That fear was confirmed when Charen was told he had primary sclerosing cholangitis (PSC), what he refers to as a “no cause-no cure disease.”

http://www.burlingtoncountytimes.com/gift-of-life/article_2f4a0898-a9dc-536e-84be-4a8f0a90ac0a.html

12 May 2014 - High IgG4 levels among primary sclerosing cholangitis patients indicated shorter time to Liver Transplant - Patients with primary sclerosing cholangitis and high immunoglobulin G4 levels were more likely to require liver transplantation than those with normal levels and had a shorter time to transplantation, according to new data presented at Digestive Disease Week 2014.


12 May 2014 - Shire acquires rare disease group Lumena - London-listed drugmaker Shire has spent an initial $260m (£153m) acquiring US biotech company Lumena Pharmaceuticals, which is trialling treatments for rare liver diseases.

http://www.telegraph.co.uk/finance/newsbysector/pharmaceuticalsandchemicals/10825109/Shire-acquires-rare-disease-group-Lumena.html

12 May 2014 - ‘Elena was my inspiration, I thought she was invincible’ - Aasma Day talks to a Preston woman battling the same condition who is involved with a support group for sufferers about why Elena was a true inspiration.

http://www.lep.co.uk/news/elena-was-my-inspiration-i-thought-she-was-invincible-1-6612083

13 May 2014 - Shire boosts rare disease portfolio with $260m Lumena deal - Shire - which has itself been the subject of merger speculation with Allergan - said buying Lumena would provide two drugs in mid-stage clinical trials for rare liver diseases that will complement its own gastrointestinal drug portfolio.

http://www.pmlive.com/pharma_news/shire_boosts_rare_disease_portfolio_with_260m_lumena_deal_568172
References:

http://www.patient.co.uk/health/primary-sclerosing-cholangitis

http://www.patient.co.uk/doctor/primary-sclerosing-cholangitis-pro

http://en.wikipedia.org/wiki/Primary_sclerosing_cholangitis

http://www.britishlivertrust.org.uk/liver-information/liver-conditions/primary-sclerosing-cholangitis/

http://www.mayoclinic.org/diseases-conditions/primary-sclerosing-cholangitis/basics/definition/con-20029446


http://www.liverfoundation.org/abouttheliver/info/psc/ (4 Oct 2011)


http://www.medicinenet.com/primary_sclerosing_cholangitis_psc/article.htm (23 Apr 2014)

Support / Blogs:

http://www.livingwithpsc.org/forum?page=2

http://www.pscsupport.org.uk/

http://www.pscpartners.org/20s30s

http://mypscstory-ben.moonfruit.com/

http://markchatterley.wordpress.com/

http://patsnewliver.blogspot.co.uk/