As early as 1939 S. Z. Levine and his co-workers\(^\text{1}\) showed that premature infants fed a high-protein diet excreted p-hydroxyphenylpyruvic acid and p-hydroxyphenylactic acid in their urine. It is now well known that raised levels of tyrosine in the serum, together with tyrosuria, occur frequently in newborn infants, especially if they are premature (neonatal tyrosinaemia, hyperphenylalaninaemia of premature infants). In a study\(^\text{2}\) of 15,000 infants severe tyrosinaemia was detected in 30% of the premature and mild tyrosinaemia in 10% of the full-term infants. This type of tyrosinaemia is more likely to arise when the infant's intake of protein is high, and it usually responds dramatically to a reduction in protein or the addition of ascorbic acid to the diet. In any case, it usually clears spontaneously a week or so after birth. It is known that p-H.P.A. oxidase is only minimally active in foetal liver, the activity increasing fivefold at term and thirtyfold in adults.\(^\text{3}\) The accumulation of p-H.P.A. itself inactivates the enzyme,\(^\text{4}\) which requires the presence of ascorbic acid or other reducing agents to maintain its activity.\(^\text{5}\) The serum tyrosine may rise as high as 30 mg per 100 ml, but from a careful study of newborn babies receiving various protein intakes M. E. Avery and colleagues\(^\text{6}\) concluded that the condition is generally harmless and that no consistent clinical syndrome is associated with the raised tyrosine level. Since an occasional infant with tyrosinaemia was lethargic, these authors considered that the needs of each infant should be considered individually.

In addition, infants of low birth weight who had tyrosinaemia had been assessed at intervals up to 56 months after birth to determine whether raised tyrosine levels had any long-term effects.\(^\text{7-11}\) No more developmental or neurological abnormalities were found than in infants with normal tyrosine levels. However, it has been suggested that, since high intakes of protein are unnecessary, they should be avoided in the feeding of premature infants,\(^\text{12,13}\) who should be given additional ascorbic acid after the first week of life.\(^\text{14}\) Occasionally tyrosinaemia in the newborn may persist for some weeks (transient hyperphenylalaninaemia). Surveys\(^\text{15,16}\) have shown that it occurs in 1 to 1.5% of full-term infants and sometimes may persist for 10 weeks or so, even in babies receiving only a moderate intake of protein. It is not reversed by extra ascorbic acid. In general transient hyperphenylalaninaemia appears to be harmless. Though several reports\(^\text{17-21}\) describe individual patients with various signs and symptoms in association with it, at present it is not clear how they are related.

The differentiation of prolonged transient hyperphenylalaninaemia from tyrosinosis is not easy in early life. In view of the beneficial effect of diet in true tyrosinosis, P. W. K. Wong and colleagues\(^\text{22}\) have suggested that it is logical to employ dietary treatment in cases of doubt and check the need for it periodically by adding protein to the diet. They consider that if abnormalities recur after the age of 10 months a diagnosis of tyrosinosis may justifiably be made.

With the increasing use of screening tests on the blood of infants, in particular for phenylketonuria, patients with neonatal tyrosinaemia and transient tyrosinemia will be recognized more frequently. It must be emphasized that synthetic diets deficient in essential amino-acids are potentially dangerous and should be given only when tyrosinosis is a real possibility. The patient must be under continuous review, and skilled dietary advice and careful laboratory control are essential.

### Cholestasis and Cholangitis

Various terms have been used to describe the syndrome comprising jaundice of an obstructive type, itching, pale stools, and dark urine, but in which the main bile ducts outside the liver are patent. One of the commonest is intrahepatic cholestasis. In the Humphry Davy Rolleston lecture published in this issue of the *B.M.J.* at page 515 Professor Sheila Sherlock describes the different diseases which may lead to this type of jaundice as the "chronic cholangitides."

The exact site at which the intrahepatic biliary passages are affected varies. She defines the cholangiole as that portion of the intrahepatic bile tree which extends from the smallest canaliculus between the liver cells to the main septal bile ducts. It includes the ductule, or canal of Hering, leading from the canaliculus to the interlobular bile duct, which is the first duct to be accompanied by a branch of the portal vein and hepatic artery in the portal tract. The interlobular bile ducts form the septal bile ducts. These join together to form the right and left main hepatic ducts, which emerge from the liver at the porta hepatis.

In many conditions of cholestasis lesions may be present in both intrahepatic and extrahepatic parts of the biliary tree. This is true for primary and secondary sclerosing cholangitis. In the latter the intrahepatic bile ducts undergo a progressive sclerosis as a result of prolonged extrahepatic obstruction, usually due to gallstones, with infection in the biliary tree. This sclerotic process may explain why jaundice sometimes fails to clear after an apparently successful reconstructive operation on the large ducts. So-called "primary" sclerosing cholangitis may complicate long-standing ulcerative colitis. Radiography shows beading of the intrahepatic bile ducts and...
irregular narrowing of the larger extrahepatic passages. Intrahepatic biliary atresia is also often associated with other lesions, including atresia of the extrahepatic biliary system.

In other conditions, such as primary biliary cirrhosis and the cholestases due to a drug, the lesion is restricted to the intrahepatic part. Drug cholestases are an increasing problem. There are two main varieties. A centrilobular cholestasis without other changes may follow the administration of anabolic steroids, especially 17-alpha alkyl-substituted steroids. Though jaundice occurs in only a proportion of patients on the drug, electronmicroscopic alterations of biliary secretion can be detected in all. Cholestasis with a nonspecific hepatitis comprising portal inflammation and hepatic necrosis is the second main kind, and is usually due to chlorpromazine or other phenothiazine derivatives. It has also resulted from taking oral antidiabetic drugs, thiazides, and erythromycin estolate. The focal injury of liver cells and portal inflammation are independent of the cholestasis, and they cause the raised serum level of transaminase which is often found. Though phenothiazine derivatives often produce some clinical interference with biliary secretion, jaundice from these drugs is, in contrast to the first group, not dose-dependent; it may be a hypersensitivity reaction. Drug-induced cholestasis usually subsides quickly on stopping the drug. Sometimes it may last for several years, and then skin xanthomata may develop. However, recovery is usually complete, though Professor Sherlock mentions two cases reported in America in which biliary cirrhosis developed six and four years from the onset.

Oral contraceptives occasionally produce cholestatic jaundice. That is not surprising, because many of the oestrogen and progestogen components are substituted steroids. This complication is commoner in Scandinavia and Chile than elsewhere, and idiopathic cholestasis of pregnancy and pruritus gravidarum are also commoner there. These conditions may reflect an increased susceptibility (possibly genetic) of the biliary apparatus to the high levels of circulating oestrogens and progestogens of late pregnancy. But in some cases of contraceptive jaundice there may also be a hypersensitivity reaction.

Primary biliary cirrhosis forms a characteristic clinical and histological syndrome. Jaundice is usually preceded by pruritus, and middle-aged women are particularly affected. It is perhaps better called chronic non-suppurative destructive cholangitis. The initial lesion is in the septal and interlobular bile ducts. They are surrounded by a dense mononuclear reaction, which occasionally takes the form of a granuloma. The aetiology is unknown. Gamma M (19S) immunoglobulin can be found in the mesenchyme adjoining the damaged bile ducts. Serum immunoglobulin M (IgM) values are increased higher and in more cases than in other forms of liver disease. But these and other serological reactions are not specific.

The clinical history, physical signs, and radiological investigations, together with liver biopsy in the more difficult case, all help in the diagnosis of intrahepatic cholestasis from extrahepatic bile-duct obstruction. When inquiring about the taking of drugs the physician may obtain helpful information from the patient's general practitioner, the chemist, or a close relative, for the patient is apt to forget details. Liver function tests are often of little help.

An exploratory laparotomy is still sometimes necessary, but it should be preceded by x-ray examination by means of a percutaneous transhepatic cholangiogram. If the diagnosis remains in doubt at laparotomy, a wedge biopsy should be taken from the anterior surface of the liver and not from the inferior edge, where confusing fibrosis is often present in healthy persons, and operative cholangiography performed.

Professor Sherlock emphasizes the importance of adequate replacement therapy of the fat-soluble vitamins A, D, and K together with extra calcium to prevent the bone complications of prolonged obstructive jaundice, notably osteomalacia and osteoporosis. Unless obstruction to bile flow is complete, pruritus can usually be relieved by oral cholestyramine. This resin exchanges chloride for bile acid and results in an increased faecal excretion of bile acid. When obstruction to bile flow is complete and no bile salts reach the gut, norethandrolone can be given. This relieves itching by a mechanism at present unknown, but unfortunately it also increases the jaundice. Steatorrhoea is often present in these patients as a result of a deficiency of bile acids and will be aggravated by cholestyramine therapy. Decrease in steatorrhoea and improved nutrition may be achieved by reducing the intake of neutral fat and giving additional fat in the form of medium-chain triglycerides, which are absorbed in the absence of bile salts. Though in many cases little can be done to affect the underlying disease, much can be done to alleviate symptoms.

Intractable Pain

Despite the introduction of new and powerful synthetic analgesics, the treatment of intractable pain continues to be difficult. In patients suffering severe and continuous pain drug treatment is not always satisfactory—firstly, because pain often returns before the next dose of the drug is due, and secondly because there are many conditions, such as post-herpetic neuralgia, which are benign and do not shorten life and in which, therefore, treatment with opiates or with other powerful analgesics is contraindicated because of the danger of addiction. Surgical methods of pain relief are often effective, but posterior root section and antero-lateral chordotomy are major neurosurgical procedures not lightly undertaken in the chronically ill and elderly. Furthermore, chordotomy has the disadvantage that the complications of bilateral operation, particularly defective sphincter control, are greater than those of the unilateral procedure. The operation cannot also be recommended with confidence for pain in the arm, while it is certainly of no value for intractable pain in the head and neck. Stereotaxic thalamotomy is now being used increasingly, but the indications for and the results of this procedure cannot yet be fully assessed.

Hence in many cases the treatment of choice for intractable pain consists of the interruption of peripheral nerves or nerve roots by means of chemical agents. M. Swerdlow has recently described his experience of cases treated at the Pain Clinic in the Salford Group of Hospitals during the period 1963 to 1966. During this four-year period 187 patients were treated, including those with cancer, post-herpetic pain, intermittent claudication, trigeminal neuralgia, post-traumatic neuritis, causalgia, and Paget's disease. The method used was either to block individual peripheral nerves with absolute alcohol or with 6% phenol in water, or, more often, to block

Swerdlow, M. Anaesthesia. 1967, 22, 568.