with β-thalassaemia as in normal individuals. Encouragingly, however, new techniques for breaking up the genes by the use of enzymes may allow the genes of patients with β-thalassaemia to be distinguished from normal genes. But this work is at an early stage and is applicable for the diagnosis of β-thalassaemia only in certain populations. More encouraging is the recent observation that this approach can accurately identify fetuses homozygous for sickle-cell anaemia.

The production of human proteins is the first tangible benefit from genetic engineering. One drug company is already testing in patients human insulin produced from bacteria, and other products are in the pipeline. Dr D Denner, of Eli Lilly Company, who has experience of trying to produce insulin on a commercial scale, thinks that the prospects for producing drugs by genetic engineering methods lie in making larger quantities of familiar hormones and enzymes rather than new drugs. Nevertheless, Professor D Hopwood from Norwich thought that genetic engineering could help eventually in developing new antibiotics. He pointed out that, unlike hormones and enzymes, antibiotics were not pure gene products but metabolites resulting from reactions with many different steps. But many of the techniques applied to *E coli*—the usual model of molecular biologists—could be applied to streptomycetes, the micro-organisms that produce most of our present antibiotics; and new antibiotics might eventually result.

One problem that overhangs this exciting work is that of regulation. In the early days of genetic engineering governments and scientists were worried that something dreadful—such as bacteria resistant to all antibiotics, or cancer-causing organisms—might result from this tinkering with the very stuff of life. Consequently, strict regulations were evolved: there were elaborate rules on physical and biological containment (biological containment consists in manipulating bacteria in such a way that they cannot survive outside controlled conditions in the laboratory). But, as Professor John Paul observed, the dangers are now seen to be those of the organism that is being used—thus elaborate precautions are essential for containing the smallpox virus but not *E coli*. Controls are now being relaxed; but he did point out that agreements are needed to limit the use of genetic engineering in making biological weapons. Let us hope that this "biological breakthrough" is not used for harm as the "atomic breakthrough" was. Even for the medical uses of genetic engineering, the complex ethical questions should be answered before and not after the techniques have been developed.

Primary pulmonary hypertension

Primary pulmonary hypertension, first described clinically by Paul Wood,[1] is a rare, progressive, and usually fatal disease which is more common in women.[2–4] The diagnosis can be made only by excluding the many causes of secondary pulmonary hypertension, starting with left ventricular failure, remembering aortic stenosis, and working back through mitral valve disease and left atrial tumour to congenital anomalies of the pulmonary veins, including cor triatriatum and supravalvar stenosing ring. Precapillary pulmonary hypertension may conceal congenital septal defects. Rarely fibrosing aveolitis or advanced sarcoidosis may present with severe pulmonary hypertension. In many tropical countries pulmonary bilharziasis closely simulates primary pulmonary hypertension, but in Britain pulmonary thromboembolism and veno-occlusive disease are the main differential diagnoses.

At the extremes of age the sex incidence is roughly equal, but most patients with primary pulmonary hypertension are women in the childbearing years. Pulmonary hypertension is usually severe by the time symptoms develop. Patients frequently present with syncope on effort. All of them are breathless, and they tend to show slight cyanosis. Considerable central cyanosis may be seen in a few patients with advanced disease who may shunt blood from the right to the left side of the heart if the foramen ovale is patent; peripheral cyanosis may be severe in patients with a very low cardiac output.

The disorder may be missed until far advanced because the physical signs are sometimes subtle and hard to elicit—even by the expert unless aided by the electrocardiogram and chest radiograph. Regular rhythm is usual; a giant venous *a* wave in the neck may be provoked but is often absent at rest; and there may be a parasternal heave, a right atrial beat, and a loud, even palpable, pulmonary closure sound. An ejection click can usually be heard at the left sternal edge if the patient holds his breath in expiration. Splitting of the second sound with respiration remains normal until the right ventricle starts to fail, when pulmonary closure becomes delayed in relation to a relatively early aortic valve closure. A diastolic murmur of pulmonary regurgitation and a murmur of tricuspid regurgitation, often misleadingly loud, may appear. The electrocardiogram usually shows sinus rhythm with right axis deviation and almost invariable T wave inversion in the right-sided chest leads. Voltage changes indicating right ventricular hypertrophy vary from slight to extreme, probably reflecting the duration of the disease. Chest radiographs often show a normal sized heart but with a dilated main pulmonary artery trunk and perhaps increased transradiancy of the lung fields caused by narrowing of the peripheral branches of the pulmonary artery. Later on in the illness the right heart chambers dilate, but sudden death may occur before heart failure develops.

Exercise tolerance is appreciably diminished with an increased pulse-to-work ratio, hyperventilation, and often a fall in blood pressure (the stroke volume does not rise to maintain blood pressure in the face of vasodilatation in exercising muscles)—the usual mechanism of syncope. Loss of consciousness may mistakenly be attributed to secondary cardiac arrhythmias; even epilepsy has been mimicked in some cases.

The echocardiogram is useful in excluding silent mitral stenosis as well as in showing a normally contracting left ventricle and dilatation of the right ventricular outflow tract. There may be increased thickness of the ventricular septum and of the anterior right ventricular wall as well as absence of the *a* wave in the pulmonary valve echo and an increased pulmonary ejection time shown by prolonged opening of the pulmonary valve. Prolapse of the mitral valve is occasionally seen; it may be attributed to the diminished size of the "starved" left ventricle. Cardiac catheterisation shows a high pulmonary artery pressure, frequently at or about systemic level when the disease is first recognised. A pulmonary wedge pressure reading may be difficult to obtain but this or the directly measured left atrial pressure is normal. The cardiac output is usually low. Pulmonary angiography shows normal anatomy but with dilated proximal branches, and macroangiograms may show the peripheral attenuation of small vessels—which accounts for the blackness of the lung fields in *x*-ray films.

Cardiac catheterisation and angiography have a purpose in making or confirming the diagnosis and in excluding other causes of pulmonary hypertension, particularly thromboembolism, in which major pulmonary artery branches will be seen to be occluded. The procedure carries some risk—normally, the adverse effect of possible vagally induced bradycardia and peripheral vasodilatation caused by contrast media.[5] These hazards may be reduced by prophylactic treatment with atropine and with phenylephrine immediately before or with the contrast injection.

Pulmonary arterial hypertension may develop secondary to thrombotic occlusion of pulmonary veins and venules.[6] This form of secondary pulmonary hypertension occurs at any age but is most common in childhood and pursues a more rapid and routinely fatal course than does the primary form. Pulmonary veno-occlusive disease may be suspected when a patient with unexplained pulmonary hypertension has a hazy background in the plain chest radiograph. Clouding may be patchy or the films may suggest pulmonary venous hypertension or interstitial pulmonary fibrosis. Intrinsic lung disease may be excluded by pulmonary function tests and other causes of pulmonary venous hypertension by echocardiography and cardiac catheterisation. Lung biopsy will confirm the diagnosis, but the possible hazards of this procedure must be weighed against a negligible gain—knowledge of the dismal prognosis—since there is no treatment known to influence the course of pulmonary veno-occlusive disease.

The aetiology of primary pulmonary hypertension is unknown but is probably diverse. An association with pregnancy or female hormones is apparent from the sex and age of most patients, but the mechanisms are unknown.[7] A familial tendency is not uncommon especially in childhood.[8] An association has been noted with Raynaud's phenomenon[9] and with connective tissue disorder, particularly the so-called "mixed connective tissue disease," and very rarely also with cirrhosis of the liver.[10] An epidemic of primary pulmonary hypertension in Switzerland a few years ago was attributed to the use of the slimming drug aminorex fumarate,[11] which has chemical similarities with the crotalaria alkaloids (present in ragwort), which can induce pulmonary hypertension in rats. Though pulmonary microembolism has been suggested as a cause of primary pulmonary hypertension (in contrast with macroembolism in large vessel thromboembolic pulmonary hypertension), there is no evidence to support this and the uniform perfusion found on lung scans is against it.[12]

The usual clinical course is progression from the onset of symptoms to death within two to 10 years, but survival for much longer periods has been reported[13 14] as also has regression of pulmonary hypertension even from an advanced stage.[15] These examples of regression could not be ascribed to treatment, and none has shown itself to be effective. Anticoagulants have been given, partly because of the microembolism theory and partly because the low cardiac output predisposes to late thromboembolic complications. Some patients show a fall in pulmonary artery pressure in response to the injection of acetylcholine directly into the pulmonary artery[16]; on that basis many vasodilator substances have been tried for long-term treatment of these patients, but all dilate the systemic vascular bed and may cause a dangerous drop in blood pressure. Drugs used have included isoprenaline, tolazoline, hydralazine, diazoxide, and nifedipine. Long-term oxygen treatment may have a limited place. More radical and more dangerous but equally useless have been sympathectomy and the creation of a shunt at atrial level (on the basis that patients with a reversed interatrial shunt survive longer).

Nevertheless, the fact that seemingly spontaneous regression of pulmonary hypertension does occur, however rarely, encourages the search for an effective treatment. Unhappily, the exciting thought of using prostaglandins in these patients has proved disappointing; research continues.

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Management of hepatic encephalopathy

The importance of the normal functions of the liver becomes clear when disease interferes with them. The fluid and electrolyte balances become disturbed, leading to ascites, oedema, hypovolaemia, and hypokalaemia, often in association with renal impairment. Haemorrhage may occur from oesophageal varices and be exacerbated by deficiency of clotting factors. Hypoglycaemia may be troublesome. The patient is unusually susceptible to infections.

Some of the most striking changes are those affectingmental and nervous function. The exact cause of hepatic encephalopathy remains problematical, but its management is of prime importance in many patients with liver failure. Hepatic encephalopathy comprises various disturbances, including paraplegia, Parkinsonism, dementia, and different types of clouding of consciousness. There is no pathognomonic anatomical brain lesion, though oedema and astroglial proliferation are characteristic.

Three patterns of hepatic encephalopathy are recognisable. Firstly, portasystemic encephalopathy results from shunting round the liver of venous blood from the gut; it is often secondary to cirrhosis or may be surgically induced. Secondly, patients with established cirrhosis may develop temporary encephalopathy in association with an infection, injudicious drug treatment, or gastrointestinal bleeding. Finally, fulminant hepatic failure may follow viral hepatitis, drug-induced