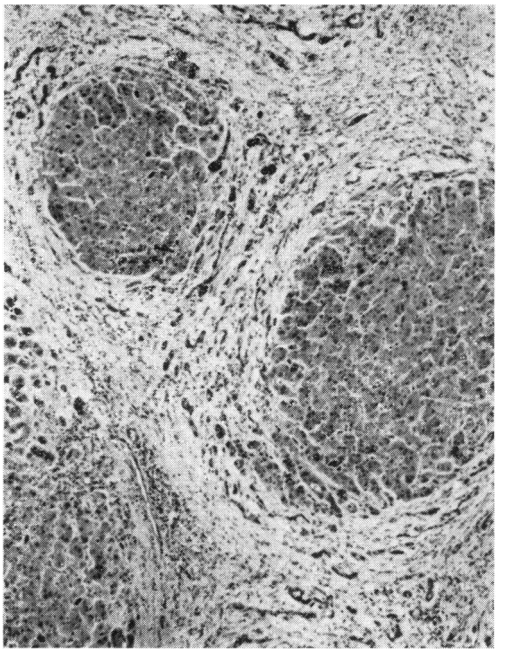

Fig 4 *Stage 4. There are regeneration nodules and broad fibrous septa. H & E×32*

biliary cirrhosis, has led to doubts as to the specificity of the disease process. Even in the cirrhotic stage, however, reduction in the number of ducts may enable a tentative retrospective diagnosis to be made.

Primary biliary cirrhosis, then, must be regarded as a pathological entity. It is by no means certain that it represents a single ætiology. Whilst some cases of the disease have been ascribed to drugs (Foulk *et al.* 1964) no agent has been shown to account for a substantial proportion of cases. The occasional finding of somewhat similar bile duct lesions in other diseases, including large duct biliary obstruction, strengthens the impression that primary biliary cirrhosis represents a pathogenetic mechanism initiated by a variety of factors.

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The Liver and Lactic Acidosis

Lactic acidosis is a condition in which abnormal amounts of lactate accumulate in the blood. As Tranquada *et al.* (1966) have stressed, the definition of lactic acidosis remains arbitrary. At the pH of body tissues and blood, lactic acid is completely dissociated and the production of lactate is accompanied by an equivalent formation of hydrogen ion. Thus any significant elevation of the blood lactate indicates that a substantial production of hydrogen ion has also taken place. It therefore seems reasonable to call the condition in which a high blood lactate persists 'lactic acidosis', regardless of resultant pH or bicarbonate levels. Tranquada *et al.* (1966) take an arterial or venous level of >7 mM as indicating lactic acidosis. They point out that this level represents a severe accumulation of lactate and is associated with a very high mortality when it occurs more than transiently. The steady-state level of lactate in arterial blood of the normal resting subject is about 1mM (Huckabee 1961*a*). (Note: Throughout this paper the term 'lactate' refers to the naturally occurring L-lactate isomer).

Since Huckabee (1961*b*) published his series of 9 fatal cases of lactic acidosis, much interest has been aroused in this condition. Tranquada (1964) reviewed the literature and collected 70 cases. Since then his own group have described their own series of 46 cases (Tranquada *et al.* 1966).

Many suggestions have been put forward as to why lactic acid accumulates in these patients, but no definite conclusions have been reached. In this paper a possible explanation will be advanced, based on current knowledge of the quantitative aspects of lactate metabolism.

The abnormal accumulation of any metabolite in the blood is evidence that the rate of its production has exceeded the rate of its disposal. In the normal human subject, the only tissue cells which are known consistently to produce lactic acid are the erythrocytes. It has been estimated that these cells produce about 25g lactate per day (Krebs 1964). Skeletal muscle is probably the other major source of lactic acid in the normal subject, but moderate steady-state exercise does not lead to accumulation of lactate in the blood (Bock *et al.* 1932). There is usually a sharp rise in blood lactate when exercise commences, but it has been demonstrated that men can work at up to two-thirds of their maximum metabolic rate without further increase in blood lactate levels

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(Margaria & Edwards 1934). As Peters & Van Slyke (1946) point out, if lactic acid were a regular intermediate product of carbohydrate metabolism of muscle, its concentration in the blood might be expected to increase somewhat when its formation was accelerated by work of this magnitude. In fact there is evidence that the exercising muscle may remove lactate from the blood (Stainsby & Welch 1966).

Under certain circumstances the liver can add lactic acid to the blood (Berry & Scheuer 1967). In the experimental animal rates of release equivalent to between 100 and 200 μg/g/min have been recorded. Thus it is feasible that the liver could discharge its complete carbohydrate store in a few hours, assuming a glycogen content of 5% (MacIntyre *et al.* 1941). Although all other tissues have the capacity to produce lactic acid under anærobic conditions, the rates of production for most tissues are not known. A limiting factor must be the availability of precursors of lactic acid. The carbohydrate in the body of a 70 kg man in the post-absorptive state amounts to about 330g (Peters & Van Slyke 1946), and this represents the maximum amount of lactic acid that could be formed from carbohydrate in the implausible event that no ærobic breakdown of glycogen or glucose was occurring. In man no pathway exists for the conversion of fat to lactic acid and there is no evidence that significant quantities are formed from protein.

Data on rates of lactate uptake are also sparse. A measure of the rate at which the human subject disposes of lactate can be obtained with the lactate tolerance test, in which 5g of lactate administered intravenously to a normal subject is cleared from the blood in about 30 min, equivalent to a clearance rate of 240g per day (Soffer *et al.* 1938). There is no doubt that extrahepatic tissues can take up considerable amounts of lactic acid. Using eviscerated cats, Long & Horsfall (1932) found that 200 mg lactate/kg/h disappeared from the blood. Similar figures were obtained by Drury *et al.* (1955) with rabbits. These values were obtained in animals which had blood lactate levels above 10 mM as a result of the operative procedure. The true rates of extrahepatic lactate uptake in the intact animal may therefore be rather less than this. Nevertheless, these figures suggest that extrahepatic lactate uptake could possibly reach 100g per day in a 70 kg human subject.

Experiments with rats have demonstrated that the liver from a fed animal can take up about 0·5 μmole lactate/g/min (Schimassek 1963). The corresponding figure for fasted rats is 2·0 μmole/g/min (Exton & Park 1966, Hems *et al.* 1966). In the fed animal about 60% of the lactate removed was converted to glucose; in the fasted animal lactate was converted almost quantitatively to glucose by the liver (Exton & Park 1966). These rates would represent a lactate uptake of about 100g per day in the fed human subject and 400g per day in the fasting individual. This correlates well with a recent study of hepatic uptake in exercise (Rowell *et al.* 1966) in which values of about 5g per hour were obtained in fed human subjects.

From these data it appears that the liver is the most important organ concerned with the uptake of lactate from the blood. Moreover the figures imply that the capacity of the liver to take up lactic acid greatly exceeds the capacity of other tissues to produce it. This means that hyperlactatæmia would not occur in the presence of normal hepatic uptake of lactate, even if no extrahepatic lactate uptake was occurring.

If the normal liver can dispose of all lactic acid which is presented to it, even when extrahepatic lactic acid production is maximal, it follows that a prolonged rise in blood lactate levels would be expected only in the presence of hepatic dysfunction. There is a substantial body of supporting evidence for this supposition. Thus, Huckabee (1961*a*) found the blood lactate to be normal in 96 patients suffering from a variety of diseases, including acute infection, chronic pulmonary disease, severe anæmia, myocardial infarction, cerebrovascular accidents, renal disease, diabetes and carcinoma. Although he noted a normal blood lactate in 5 patients with hepatic disease, there have been several reports where the blood lactate has been raised (e.g. Adler & Lange 1927, Noah 1927, Hochrein & Meier 1928, Jervell 1928, Schumacher 1928, Mizuno 1931, Snell & Roth 1932, Mulhausen *et al.* 1967). These instances include many examples of patients with fulminating liver disease with blood lactate levels above 10 mM who could be described as suffering from lactic acidosis. There is also good evidence that the lactate tolerance test is impaired in liver disease (Soffer *et al.* 1938). Moreover, by administration of adrenaline it has been demonstrated that subjects with liver disease remove endogenous lactate from the blood more slowly than do normal subjects (Nitzesco & Gontzeu 1935, Nalebuff & Winternitz 1956).

There are other circumstances apart from parenchymal cell necrosis in which the liver may fail to remove circulating lactate from the blood. In shock due to hæmorrhage or endotoxin the splanchnic blood flow may be greatly reduced (Corday *et al.* 1962) so that hepatic lactic acid uptake is grossly impaired. Hepatic arterial blood flow may also be markedly diminished consequent on the fall in arterial pressure which accompanies hypocapnia (Cohn & Kountz 1963). Since the hepatic artery appears to be the chief source of oxygen supply to the liver (Blalock &

Mason 1936), a fall in blood flow through the artery could readily lead to hypoxia of the parenchymal cells. A low blood P_{CO_2} may be induced by forced ventilation with a mechanical respirator or by a primary stimulation of the respiratory rate. In each circumstance a rise in blood lactate has been recorded (Berry & Scheuer 1967, Eichenholz *et al.* 1963). If hepatic blood flow is grossly impaired the liver may actually add lactic acid to the blood as the hypoxic liver cells undergo anærobic glycolysis (Berry & Scheuer 1967).

Even in the absence of reduced hepatic blood flow hypocapnia may act in another way to bring about a raised blood lactate. An alkalotic pH stimulates glycolysis in erythrocytes (Tsuboi & Fukunaga 1965) and muscle (Opie *et al.* 1963), and can also bring about a changeover from lactate uptake to lactate output by the liver (Berry & Scheuer 1967). Other types of biochemical lesions or metabolic changes within the liver cell may also be expected to lead to a rise in blood lactate levels. It is probable that the hyperlactatæmia accompanying certain forms of glycogen storage disease is related to the release of hepatic glycogen stores as lactic acid in the absence of a pathway for glucose release (Oei 1962).

Certain drugs may disturb hepatic lactate metabolism. A number of cases of lactic acidosis have been associated with the administration of the drug phenformin (Tranquada *et al.* 1963, Bernier *et al.* 1963, Lacher & Lasagna 1966), and there is experimental evidence that phenformin inhibits the uptake of lactate by the liver (Patrick 1966). Alcohol is known to shift the redox potential of the liver cell to a more reduced level (Lundquist *et al.* 1962) and it has been demonstrated that administration of alcohol impairs lactate tolerance (Daughaday *et al.* 1962). An acidotic pH may also lead to inhibition of lactate uptake by the liver. Experiments have shown that if the pH of the perfusing medium falls below 7·1, uptake of lactate by the isolated perfused rat liver is reduced tenfold (Hems *et al.* 1966). Finally, it is possible that under certain conditions the permeability of the parenchymal cell membrane to lactate may be reduced with a resultant impairment of lactate uptake.

The great majority of cases of idiopathic lactic acidosis described in the literature can be accounted for on the basis of one or other of these mechanisms (Tranquada 1964). However, only about 40% of cases have overt liver pathology (Tranquada *et al.* 1966). Nevertheless, in the present state of our knowledge it would seem advisable to regard every patient suffering from lactic acidosis as a potential case of hepatic failure.

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