DRUG METABOLISM IN LIVER DISEASE

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SUMMARY

Drug Metabolism in Liver Disease

This thesis describes investigations into the metabolism and excretion of different drugs in healthy subjects and patients with acute and chronic liver disease.

Following oral administration the plasma concentrations and plasma half-lives of paracetamol, antipyrine and lignocaine were measured in healthy subjects and patients with chronic liver disease. In the patients there was a substantial increase in the systemic bioavailability of lignocaine; the increase being less marked with paracetamol whilst antipyrine showed no such increase. The plasma half-lives of all three drugs were significantly correlated with the vitamin K_1-corrected prothrombin time ratio and the serum albumin but not with the serum bilirubin, alkaline phosphatase or alanine aminotransferase. There were significant correlations between the plasma half-lives of all three drugs. The plasma lignocaine half-life was always prolonged to a much greater extent than that of paracetamol or antipyrine and was a highly sensitive indicator of hepatic dysfunction.

In patients with decompensated liver disease given 1 gm of paracetamol 8 hourly for 3 days there was no evidence of accumulation of paracetamol in the plasma and no reduction in the excretion of the mercapturic acid and cysteine conjugates.

The plasma lignocaine and antipyrine half-lives were measured simultaneously in patients with chronic liver disease before and after 5 days treatment with phenobarbitone, before and after prednisolone therapy and in patients with cirrhosis before and after porto-systemic shunting. Phenobarbitone produced no significant change in either drug half-life but a marked reduction in the half-lives of both drugs was seen following prednisolone therapy. Following porto-systemic shunting the plasma half/

half-lives of both drugs were prolonged in most of the patients.

The plasma antipyrine half-life was measured in patients with paracetamol-induced acute hepatic necrosis and subsequently on recovery. Initially 60% of the patients had a prolonged half-life there being significant correlations between the antipyrine half-life, the paracetamol half-life and the alanine aminotransferase on the day of the study. The antipyrine half-life had returned to normal 7 - 63 days later.

The studies show that the metabolism of drugs in patients with liver disease depends on the physico-chemical properties of the drugs as well as the nature and severity of the liver disease.

The thesis comprises four sections:

SECTION I — Introduction and Historical Review.

SECTION II — Paracetamol, antipyrine and lignocaine metabolism and excretion in healthy subjects and patients with chronic liver disease.

SECTION III — Lignocaine and antipyrine metabolism in patients with chronic liver disease before and after phenobarbitone and prednisolone therapy and porto-systemic shunting.

SECTION IV — Antipyrine elimination in paracetamol-induced acute hepatic necrosis.

CONTENTS OF THESIS

SECTION I

INTRODUCTION & HISTORICAL REVIEW

INTRODUCTION & HISTORICAL REVIEW

The liver is the major site of metabolism of many drugs, foreign compounds and endogenous substances such as bilirubin, thyroxine and various steroid hormones (Conney, 1967). The metabolic transformation of these different compounds is achieved by enzymes which usually convert a lipid-soluble compound to metabolites which are more water soluble and thus more readily excreted in urine or bile. Many of these enzymes are located in the smooth endoplasmic reticulum (Brodie, Gillette & La Du, 1958) a fine network of cytoplasmic membranes in the hepatocyte which, on cell fractionation, constitutes the microsomes. Here, depending on the particular substrate, a variety of metabolic reactions takes place, the most important of which are oxidation, N-dealkylation, hydroxylation, reduction, de-esterification and conjugation.

There are two major enzyme systems responsible for drug metabolism. The first is the mixed function oxidase system which mediates preconjugation or phase I reactions which serve to append or reveal suitable chemical groupings such as OH, NH_2 and COOH within the drug. These reactions are mediated by an organised sequence of enzymes of the smooth endoplasmic reticulum. One of the most important enzymes in this reticulum is cytochrome P-450 which constitutes up to 20% of the protein of the endoplasmic reticulum (Estabrook et al., 1971). This system transfers electrons from NADPH to flavoproteins, iron-containing enzymes and finally to a ferric haem enzyme, cytochrome P-450, which is reduced by cytochrome P-450 reductase to form ferrous cytochrome P-450. This new complex avidly combines with free oxygen to form a substrate which has a high affinity for a wide range of compounds. Once the drug combines with this substrate it is hydroxylated and the haem moiety is oxidised to ferric cytochrome P-450 which re-enters the cycle (Mannering, 1971).

The second major group of enzyme systems involved in drug metabolism cause conjugating or phase II reactions in which groupings revealed by/

by phase I reactions are coupled to endogenous compounds such as glucuronic acid and sulphate. This tends to abolish the pharmacological action of the drug and render the drug conjugate more water soluble and thus more readily excreted in urine or bile. The commonest conjugate is glucuronic acid derived from glucose-1-phosphate which is synthesised into uridine diphosphate glucuronic acid (UDPGA) by enzymes in the supernatant fraction of the cell. UDPGA interacts with an acceptor compound under the influence of the microsomal enzyme glucuronyl transferase (Isselbacker, Chrabas & Quinn, 1962). Alternative conjugating moieties can be donated from a variety of enzyme systems located in different parts of the liver cell. These include sulphates and various amino acids. Other processes involved are acetylation and methylation.

As the liver is the major site for drug metabolism it might therefore be expected that this process would be abnormal in patients with liver disease. Many studies, however, have failed to show a consistent relationship between liver disease and altered drug disposition; liver disease seeming to affect the elimination half-life of some drugs which undergo extensive hepatic transformation, but not others. For example, the plasma half-lives of salicylic acid, aminopyrine and dicoumarol (Brodie, Burns & Weiner, 1959), chloramphenicol (Held & von Olderhausen, 1971), chlorpromazine (Maxwell et al., 1972) and diphenylhydantoin (Blaschke et al, 1975) have been reported to be normal in patients with liver disease whilst the half-lives of amylobarbitone (Mawer, Miller & Turnberg, 1972), lignocaine (Thomson, Rowland & Melmon, 1973), carbenicillin (Hofmann, Cestero, & Bullock, 1970), diazepam (Klotz et al, 1975), clindamycin (Avant, Schenker & Alford, 1975), pethidine (Klotz et al, 1974; McHorse et al., 1975), prednisone (Powell & Axelsen, 1972), rifampicin (Acocella et al, 1972) and isoniazid (Levi, Sherlock & Walker, 1968) have been noted to be abnormal in such patients.

In addition, in patients with liver disease normal and abnormal plasma half-lives of the same drugs have been reported by different workers.

Thus both normal and abnormal rates of elimination of antipyrine (Brodie, Burns & Weiner, 1959; Branch, Herbert & Read, 1973; Andreasen et al., 1974; Andreasen & Vessell, 1974; Burnett et al, 1976), pentobarbitone (Sessions et al, 1954; Ossen burg et al, 1973), phenylbutazone (Weiner, Chenkin & Burns, 1954; Brodie, Burns & Weiner, 1959; Levi, Sherlock & Walker, 1971; Hvidberg , Andreasen & Ranek 1974) and tolbutamide (Veda et al, 1963; Nelson, 1964) have been reported in such patients. Although these discrepancies may, in part, be due to a failure to discriminate between acute and chronic liver disease and the extent and severity of the disease there are many other factors which have been shown to affect the rate of human drug metabolism and which might also account for the observed differences in rates of drug elimination. Some of these factors are listed in Table I.

Although the majority of these factors apply only to patients with liver disease some apply equally to healthy subjects. Thus age and sex have been shown to influence the rate of drug elimination in healthy subjects and may well exert a similar effect in patients with liver disease.

The rate of removal of a drug metabolised by the liver is usually dependent on the inter-relationships between several of the factors listed in Table I such as hepatic blood flow, functional liver cell mass, drug metabolising enzyme activity and the degree of protein binding of the drug in plasma. Liver disease may affect more than one of the factors listed in Table I and this may exaggerate or reduce any effect associated with altered hepatocyte function per se.

TABLE I

FACTORS WHICH MAY INFLUENCE DRUG ELIMINATION IN LIVER DISEASE

Functional Liver Cell mass

Drug metabolising enzyme activity affected by

- Genetic factors
- Age
- Sex
- Previous and concurrent drug therapy
- Ethanol consumption
- Smoking
- Diet
- Exposure to chemicals
- Vitamin deficiency

Malnutrition

Changes in volume of distribution

Abnormal plasma protein and tissue binding

Liver blood flow

Miscellaneous conditions e.g.

- Renal disease
- Thyroid dysfunction
- Anaemia

1. Functional Liver Cell Mass

The number of functioning hepatocytes is important in determining the clearance or rate of removal of drugs from the plasma. Although usually decreased in acute hepatic necrosis and severe cirrhosis, the liver cell mass may, because of hyperplasia, be normal or increased in the early stages of cirrhosis. Thus some patients with chronic liver disease may have a normal or even an increased number of functioning hepatocytes and this may, in part, explain why such patients can apparently metabolise drugs normally.

2. Drug Metabolising Enzyme Activity

Although the rate of hepatic metabolism of drugs is dependent on the number of functioning hepatocytes it must also be dependent on the activity of the drug metabolising enzymes within each liver cell. Their activity are, in part, genetically determined but can also be affected by age and a wide range of agents such as drugs, alcohol, smoking, diet and exposure to chemicals (Conney, 1967).

These agents may cause induction, or inhibition of the microsomal enzymes. Although most reports of induction or inhibition relate to patients without liver disease, enzyme induction has been noted in patients with liver disease (Branch, Herbert and Read, 1973). The phenomenon of mammalian enzyme induction was first described by Brown, Miller and Miller (1954) who found an increase in 3,4-benzpyrene hydroxylase activity with the repeated administration of 3,4-benzpyrene. Subsequently phenobarbitone was noted to increase the rate of its own metabolism (Remmer, 1958). This increase is due to an increase in the amount of enzyme present; representing "de novo" synthesis.

a. Genetic Factors

The influence of genetics on human drug metabolism has been well documented by Vesell and Page (1968 a,b & c), by Vesell et al (1971a) and by Vesell , Page & Passanti (1971b). In studies with phenylbutazone antipyrine, dicoumarol and ethanol on fraternal and identical twins they noted that intra-twin differences in drug half-lives were appreciably greater in fraternal than identical twins. The half-lives of these drugs were the same in each pair of identical twins; although large variations in half-lives occurred amongst pairs of twins. More specifically genetic inheritance accounts for the phenomenon in the normal adult population of slow and fast acetylators of drugs such as sulphasalazine and isoniazid (Price Evans, 1968).

b. Age

A number of studies in healthy adult subjects have shown that drug elimination becomes slower with increasing age. Thus O'Malley et al (1971) found the antipyrine and phenylbutazone half-lives to be 45% and 29% greater respectively in geriatric patients with a mean age of 77 years compared with healthy volunteers with a mean age of 26 years. Jori, Disalle & Quadri (1972) found the aminopyrine half-life to be more prolonged in elderly than young subjects whilst Irvine et al (1974) noted that the hydroxylation of amylobarbitone was significantly slower in patients over 65 years than those aged between 20 and 40 years. In addition Klotz et al (1975) noted that in healthy subjects the plasma half-life of diazepam exhibited a striking age dependence; at 80 years of age being four and a half times that at 20 years of age.

In a more detailed study, however, Vestal et al (1976) showed that the half-life of antipyrine was not significantly different between two groups of normal subjects with mean ages of 33 years and 50 years; whilst a group with a mean age of 69 years had a half-life 17% longer than the/

the youngest group. However, there were significant differences between all 3 groups in the metabolic clearance rate of the drug; the oldest group having the lowest clearance and the youngest the highest. This finding is in contrast to that of Klotz et al (1975) who found that the plasma clearance of diazepam showed no significant age-dependence and that the differences in the half-life could be explained by differences in the volume of distribution (page 13). In the study of Vestal et al (1975) the antipyrine half-life correlated with age and could be predicted from the equation $T\frac{1}{2}$(hours) = 10.7 + 0.06 (age). However, when smoking habits were taken into account it was found that much of the difference in the half-life values between the young and old groups could be explained by the higher cigarette consumption in the younger age group. (page 11). Thus although protein synthesis is decreased in the elderly other factors in addition to a reduction in drug microsomal enzyme activity may, in part, account for a prolongation of the drug half-lives in these patients.

There is little information on the effects of age on rates of drug metabolism in patients with liver disease. In one study in patients with chronic liver disease Farrell et al (1978) found no correlation between the plasma antipyrine half-life and age.

c. Sex

Although a sex difference in the rate of drug metabolism in rats has been documented (Conney, 1976) there is little evidence for such an effect in man. Although the work of Vessell & Page (1968a, 1968b) suggested that for antipyrine and phenylbutazone there was a slightly lower rate of metabolism in males, Whittaker and Price Evans (1970) found no sex difference in the rate of phenylbutazone metabolism in a large group of normal subjects. O'Malley et al (1971) however, found the half-life of antipyrine to be significantly shorter in young females than young males. In contrast, the antipyrine half-life was much more prolonged in geriatric females than young females compared with the prolongation in the geriatric group as a whole over the younger group.

d. Previous and concurrent drug therapy

In therapeutic doses a number of different drugs have been shown to cause enzyme induction, namely barbiturates (Conney et al, 1960; Macdonald et al, 1969; Kampffmeyer 1971; Stevenson et al, 1972; Breckenridge et al, 1973; Branch et al, 1973), glutethimide (Macdonald et al, 1969) and diphenhydramine - methaqualone ("Mandrax") (Stevenson et al, 1972). The barbiturates produce a dose related induction of microsomal enzymes in man (Breckenridge et al, 1973). Other drugs such as corticosteroids (Branch et al, 1973), rifampicin (Acocella, 1978) anticonvulsants (Hepner et al, 1977) spironolactone (Ubshagen et al, 1977) and meprobamate, chlorpromazine, tricyclic antedepressants and phenylbutazone (Conney, 1967; Prescott 1973) also produce enzyme induction. Induction usually develops over a period of several days or weeks and persists for a similar period following withdrawal of the inducing agent.

In contrast certain drugs may cause the inhibition of metabolism of other drugs. Although this may be entirely due to inhibition of hepatic microsomal enzymes other mechanisms including substrate competition/

competition, interference with drug transport and depletion of hepatic glycogen may also be important (Prescott, 1973).

O'Malley et al (1972) reported a prolonged antipyrine half-life in patients taking oral contraceptive steroids compared with control subjects, although the phenylbutazone half-life was similar in the two groups. Oestrogens bind to rat liver cytochrome P-450 (Schenkman et al, 1967) and may therefore produce their effect by competitive inhibition. The half-life of pethidine and promazine has also been reported to be prolonged in patients taking the contraceptive pill (Crawford & Rudofsky 1966).

In man chloramphenicol has been shown to prolong the plasma half-lives of tolbutamide, phenytoin and dicoumarol and this appears to be the result of enzyme inhibition (Christensen & Skousted, 1969), whilst the increased toxicity of pethidine in patients receiving monoamine oxidase inhibitors may also be due to this mechanism (Sjöqvist, 1965). In addition the metabolism of tolbutamide in man may be slowed by several other drugs including phenylbutazone and the sulphonamides (Prescott, 1973) whilst oxyphenylbutazone has been reported to slow the metabolism of the coumarin anticoagulants (Burns & Conney, 1965).

Thus in patients without liver disease previous and concurrent drug therapy can act to alter the rate of elimination of drugs from the plasma and these drugs probably exert a similar effect in the presence of liver disease.

e. Ethanol

The effect of ethanol on the rate of hepatic drug metabolism depends on the time elapsed after acute loading and on adaptive liver changes associated with the chronic ingestion of alcohol (Sellars & Holloway, 1978). An acute alcohol load impairs the activity of the drug metabolising enzymes (Rubin & Leiber, 1968a; Ariyoshi et al, 1970) so that the plasma clearance of many drugs such as meprobamate and pentobarbitone (Rubin et al, 1970), tolbutamide (Carulli et al, 1971), chlordiazepoxide /

chlordiazepoxide (Linnoila & Matilla, 1973) and antipyrine (Schuppell & Steinhilber, 1973) are reduced.

Chronic alcohol ingestion results in proliferation of the smooth endoplasmic reticulum and an increase in the microsomal protein content and cytochrome P-450 (Rubin & Lieber, 1968b; Lieber & DeCarli 1968, Rubin & Lieber, 1968b; Rubin et al, 1968; Pirttiaho et al, 1978). This results in an increase in liver enzyme activity and an accelerated rate of metabolism of many drugs such as tolbutamide (Kater et al, 1969; Shah et al, 1972), phenytoin and warfarin (Kater et al, 1969), antipyrine (Vessell, Page & Passananti, 1971; Pirttiaho et al, 1978) meprobamate and pentobarbitone (Misra et al, 1971), as well as ethanol itself (Kater et al, 1968). Indeed in chronic alcoholics Pirttiaho et al (1978) noted a correlation between increased P-450 content and increased antipyrine clearance.

Prolonged ethanol consumption, however, can lead to hepatic damage such as a fatty liver, alcoholic hepatitis or cirrhosis. In severe hepatitis and cirrhosis cytochrome P-450 is reduced (Schoene et al 1972; Sotaniemi et al, 1977; Pirttiaho et al, 1978) and in this situation impaired metabolism of many drugs has been noted, viz. aminopyrine (Schoene et al, 1972; Hepner & Vessell 1975), antipyrine (Branch et al, 1973; Andreasen et al, 1974; Sotaniemi et al, 1977), pethidine (Klotz et al, 1974) and diazepam (Klotz et al, 1975).

In addition alcohol ingestion may affect other parameters which affect the rate of drug elimination such as distribution and protein binding (Sellars & Holloway, 1978).

f. Cigarette Smoking

Most available evidence suggests that smoking induces the microsomal enzymes. Nicotine has been shown experimentally to induce hepatic drug metabolising enzymes (Yamamoto et al, 1966) and the "in vivo" rate of metabolism of nicotine is enhanced in cigarette smokers (Beckett & Triggs 1967). Phenacetin (Pantuck et al, 1974) theophylline (Jenne et al, 1975)/

1975) and antipyrine (Vestal et al, 1975) metabolism has been shown to be increased in cigarette smokers; the increase in metabolism of phenacetin being due to enzyme induction by 3,4-benzpyrene in cigarette smoke (Pantuck et al, 1974). In contrast, however, Klotz, et al (1975) found no increase in the rate of diazepam clearance in smokers.

g. Diet

Diet, unassociated with malnutrition, may affect rates of drug metabolism in man. In this respect the most important dietary constituent is protein; animal studies having shown that there is a reduction in the level of cytochrome P-450 on low protein diets (Campbell & Hayes, 1966).

In man, fasting was found not to influence the half-lives of antipyrine or tolbutamide in obese subjects (Reidenberg & Vessell, 1975). The antipyrine and theophylline half-lives were decreased when healthy subjects were changed from their normal diet to a high protein-low carbohydrate diet (Kappas et al, 1976). Supplementation of a normal diet with carbohydrate caused an increase in the half-life of the two drugs whereas a protein supplement caused a decrease. In addition Fraser et al (1977) noted that the antipyrine half-life of Asian vegetarians in London was significantly longer than Caucasian non-vegetarians. Drug elimination may, therefore, be expected to be reduced in patients with alcoholic cirrhosis on the basis of their known low protein and high carbohydrate intake alone.

h. Chemicals

A wide range of pesticides and herbicides may produce enzyme induction (Fouts, 1970); a reduced antipyrine half-life being reported in patients exposed to dicophane (DTT) (Kolmodin, 1969).

i. Vitamin deficiency

In patients with alcoholic and primary biliary cirrhosis the antipyrine half-life was found to be significantly prolonged in those patients with vitamin C deficiency (Beattie & Sherlock, 1976). It is uncertain,/

uncertain, however, if this is secondary to an effect on the activity of the microsomal enzymes.

3. Malnutrition

Malnutrition is associated with a wide variety of changes in the body each of which may affect the rate of drug metabolism. These include and increase in total body water, a decrease in the endoplasmic reticulum, hypoalbuminaemia and a reduction in cardiac output (Krishnaswamy, 1978).

It results in a large number of deficiencies such as vitamins, iron, calcium and trace elements which, in animals, have been shown to result in altered drug metabolism (Campbell & Hayes, 1974; Campbell, 1977). There is, however, little such information in man.

In animals there have been variable effects of acute and chronic starvation on rates of drug metabolism. Thus Dixon et al (1960) reported depressed drug metabolism, Kato & Gillette (1965) increased drug metabolism whilst Basu et al (1973) noted no significant changes.

In man, also, malnutrition is not always associated with impaired drug metabolism. Thus whilst Mehita et al (1975) noted a reduced metabolism of chloramphenicol in malnourished children, Krishnaswamy & Naidu (1977) found the rate of disappearance of antipyrine to be faster in a group of undernourished subjects compared with normal subjects. Even in patients with nutritional oedema the mean antipyrine half-life was similar to the normal population. This is perhaps not surprising as there is evidence that in malnutrition liver protein is maintained at the expense of body protein (Krishnaswamy, 1978). In addition, hypoalbuminaemia may result in more free drug being available to the liver for metabolism (page 15).

4. Changes in Volume of Distribution

The rate of removal of a drug from plasma is often expressed in terms of its half-life ($T\frac{1}{2}$). This is, however, determined by two /

two independent variables, the apparent volume of distribution (V_D) and the plasma clearance of the drug as:

$$T\frac{1}{2} = \frac{0.693 \times V_D}{\text{clearance.}}$$

The volume of distribution of a drug is derived from the equation

$$V_D = \frac{\text{Dose administered}}{\text{Plasma concentration at time zero .}}$$

Thus although the volume of distribution of a drug can affect the its plasma half-life it does not affect its true rate of metabolism. The volume of distribution can be affected by changes in protein binding as well as by changes in the extracellular volume.

The volume of distribution may change with age although the evidence for this is conflicting. Thus whilst with diazepam Klotz et al (1975) found it to increase linearly with age Vestal et al (1976), with antipyrine, found it to be significantly less in younger subjects with a mean age of 33 years than older groups of subjects with mean ages of 50 and 69 years. In patients with chronic liver disease there is evidence that the volume of distribution is increased if ascites is present. Thus with d-propranolol Branch, James & Read, (1976a) noted that patients with chronic liver disease and ascites had a two-fold increase in the volume of distribution of the drug compared to similar patients without ascites whilst with ampicillin Lewis & Jusko (1975) found the volume of distribution to be larger in patients with cirrhosis and ascites compared with healthy subjects.

However, in the absence of ascites there is conflicting evidence of the effect of chronic liver disease on the volume of distribution. Andreasen et al (1974) with antipyrine and Branch, James & Read (1976a) with antipyrine and indocyanine green noted the volume of distribution of these/

these drugs to be similar in patients with chronic liver disease and normal subjects. On the other hand Thomson et al (1973) and Klotz et al (1975) noted that the volume of distribution of lignocaine and diazepam respectively was significantly greater in patients with chronic liver disease than normal subjects suggesting that liver disease per se acts to alter the volume of distribution - perhaps by an alteration in the tissue distribution or protein binding of the drugs. Whilst the differences in these studies may be due to differences in the severity of the liver disease other factors may act to influence the volume of distribution of drugs and it is possible that in any given situation that the volume of distribution of some drugs may be affected more than others.

In addition there is evidence that ascitic fluid may have different pharmocokinetic characteristics from other body tissues (Lewis & Jusko, 1975) with slow transfer of drugs in and out of the fluid (Shear, Ching & Gabuzda, 1970) and this in itself may also alter plasma drug half-lives.

5. Abnormal Plasma Protein and Tissue Binding

Liver disease alters the plasma and tissue binding of drugs (Blaschke, 1977) which can independently affect both the volume of distribution (Klotz, 1976) and the drug clearance (Wilkinson & Shand, 1975) and hence the plasma half-life. Albumin is quantitatively the most important plasma protein responsible for drug binding, but many drugs, especially basic drugs, may, in addition, be bound to other plasma proteins.

The serum albumin and thus the total number of albumin binding sites are frequently reduced in patients with acute and chronic liver disease. The magnitude and significance of changes in the fraction of bound drug produced by reduction in albumin or globulin concentrations will, however, depend on the total drug concentration, number of binding sites and dissociation constant(s) for the drug (Koch-Weser & Sellers, 1976).

In addition the hepatic extraction ratio of a drug (i.e. the fraction of the drug removed from the blood during a single transit through the liver) will determine the effect of hypoalbuminaemia on its clearance. Thus with drugs with a high hepatic extraction ratio a reduction in plasma protein binding may not affect hepatic clearance as hepatic blood flow is the major determinant of their hepatic clearance (Nies, Shand & Wilkinson, 1976). With drugs with a low hepatic extraction ratio changes in the binding of the drugs may be more important. Thus with drugs with a high affinity for plasma proteins, conditions affecting plasma protein binding might have a significant effect on their hepatic clearance whilst those with a low affinity are unaffected by conditions that produce changes in protein binding alone (Wilkinson & Shand, 1975). As the degree of plasma protein binding decreases, more of the drug is available for distribution to the tissues and hence the volume of distribution increases (Gillette, 1971; Wilkinson & Shand, 1975). This would tend to increase the drug half-life. However, as binding decreases, more of the drug becomes available in the plasma in the free form and is therefore more readily available to the liver for extraction and metabolism. This effect may increase elimination of the drug from the plasma, as has been noted in acute viral hepatitis with tolbutamide and phenytoin, (Wilkinson & Schenker, 1976).

Abnormal plasma binding has also been noted in patients with liver disease when the serum albumin concentration is normal, as in acute viral hepatitis and also where proteins other than albumin are involved; for example with d-propranolol (Branch, James & Read, 1976b). This may well be due to endogenous binding inhibitors on the albumin molecule (Reidenberg & Affrime, 1973; Wilkinson & Shand, 1975).

Increased levels of bilirubin may also alter the binding of some drugs by competitive displacement. "In vitro" addition of bilirubin has been shown to decrease the binding of phenytoin (Blaschke et al, 1975) and tolbutamide and warfarin (Williams et al, 1976a&b). In these experiments,

experiments, however, the change in binding was less than that observed in plasma from patients with liver disease again suggesting the presence of other displacing agents.

In addition to binding to plasma proteins, tissue binding of drugs is an important determinant of the distribution of drugs in the body and thus of half-life. The liver for example, contains a high concentration of an anion binding protein called ligandin which is responsible for the binding of a number of endogenous and exogenous substances such as BSP and indocyanine green and the effect of liver disease on this binding protein is unknown. In addition tissue binding of drugs may be affected by alterations in plasma or tissue pH (Brodie et al, 1950; Waddell & Butter, 1957; Garrett et al, 1974) or the presence of ascites (Lewis & Jusko, 1975; Branch, James & Read 1976b).

It must be remembered, also that altered drug binding may occur in other conditions such as renal disease, deficiency states and cardiac failure which may exist in patients with liver disease (Tillement, Lhoste & Giudicelli, 1978).

6. Liver Blood Flow

As previously noted the plasma half-life of a drug depends on the systemic clearance of the drug as well as the volume of distribution. This systemic clearance depends both on the excretion of unchanged drug via bile or kidneys and also on its rate of metabolism. Although drug metabolism takes place predominantly in the liver, it may also occur at extra-hepatic sites such as kidneys, lungs and gut mucosa.

The hepatic clearance of a drug depends on the rate of blood flow to the liver and the extent of the drug's uptake and removal or what is termed intrinsic hepatic clearance. This is dependent on the steady state arterial (Ca) and venous (Cv) drug concentrations across the liver.

Thus hepatic clearance can be expressed in terms of the hepatic flow rate Q and the extraction ratio E as:

$$QE = Q \frac{(Ca-Cv)}{Ca}$$ (Wilkinson & Schenker, 1975)

The intrinsic hepatic clearance of a drug is a measure of the ability of the liver to remove the drug from the blood. It therefore reflects a number of processes such as the uptake of the drug into the hepatocyte, rate of metabolism within the hepatocyte and the rate of biliary excretion. The efficiency of these individual processes may be impaired by hepatic pathology such as necrosis, fibrosis and/or hyperplasia, as well as by any reduction in liver blood flow. Thus it can be seen that the half-life of an extensively metabolised drug can be influenced by at least four biological factors, namely hepatic blood flow, extraction efficiency of the liver , activity of the microsomal enzymes and the volume of distribution. The volume of distribution as previously mentioned is, in turn, dependent on other factors such as plasma protein binding and ascites.

Although liver blood flow is primarily dependent on cardiac output, liver disease per se can alter the flow of blood through the liver. Patients with liver disease have varying degrees of abnormalities of portal and total hepatic blood flow dependent upon the nature, activity and severity of the liver pathology. In acute viral hepatitis normal (Preisig et al, 1966) or even slightly increased liver blood flow (Lundbergh , 1974; and Lundbergh& Strandell, 1974) has been reported. This may, in part, account for the reported increased clearance of tolbutamide (Williams et al, 1976a and phenytoin (Blaschke et al, 1975) in acute viral hepatitis. However, in this situation alterations in drug plasma protein binding may also contribute to this increase (Wilkinson & Schenker, 1976).

In chronic liver disease the available data suggests that total liver blood flow is not reduced. Although Bradley, Ingelfinger & Bradley (1952), Redeker, Geller & Reynolds (1958) and Caesar et al (1961) reported hepatic blood flow, as measured by clearance techniques, to be moderately reduced in cirrhosis Cohn et al (1972), using a more accurate indicator dilution technique, could not confirm this. In that study patients with acute alcoholic hepatitis had a significantly higher hepatic blood flow than normal subjects; those with alcoholic cirrhosis having similar flow rates to the healthy subjects. Although cardiac output is increased in cirrhosis (Kowalski & Abelmann, 1953; Cohn, et al, 1972) the hepatic fraction of the cardiac output appears to be reduced in this situation (Cohn et al, 1972).

Although total blood flow to the liver may not be decreased in cirrhosis, collateral shunts may, however, exist between the portal and systemic circulations. In addition, intrahepatic shunts occur which shunt blood away from the functional hepatocytes. Thus in patients with alcoholic liver disease (Groszmann et al, 1972) and cirrhosis (Lebrec, Kotelanski & Cohn, 1976) it was found that an average of 62% and 70% of mesenteric and 80% and 95% of splenic blood flow underwent shunting through portosystemic collaterals. In neither study was there any significant relationship between percentage shunting and hepatic blood flow or portal pressure. In similar patients intrahepatic arteriovenous anastomoses have been reported to range from 3 - 66% (Groszmann et al, 1972) and 3 - 34% (Groszmann et al, 1976). The effect of such shunting is therefore to reduce the blood supply to the hepatic cells to a greater extent than total liver blood flow estimates would indicate.

The extent to which changes in total liver blood flow will alter the rate of hepatic drug metabolism depends mainly on the hepatic extraction ratio of the drug. Thus for drugs with a high hepatic extraction ratio, for example lignocaine, propranolol and indocyanine/

indocyanine green, hepatic clearance is highly dependent on the blood flow to the liver and does not directly reflect the activity of the drug metabolising enzymes. Thus alterations in liver blood flow will greatly affect the clearance of such drugs. On the other hand drugs with a low hepatic clearance, e.g. antipyrine will be little affected by changes in liver blood flow (Wilkinson & Shand, 1975).

Thus in cardiac failure hepatic blood flow is reduced and the plasma half-life of lignocaine is greatly prolonged (Thomson et al, 1973; Prescott et al, 1976), whereas in the same patients there was relatively little prolongation in the antipyrine half-life (Prescott et al, 1976). The validity of these concepts is strengthened by the fact that in patients with portosystemic shunting indocyanine green clearance is more abnormal than antipyrine clearance (Branch, James & Read, 1976a). In addition, it has been noted that the central nervous system side-effects with the schistosomicide niridazole are increased in the hepatosplenic form of bilharziasis as compared to the intestinal form of the disease (Faigle, 1971). Plasma concentrations of the unchanged drug are elevated in these patients even though hepatic parenchymal function is well preserved. This suggests that the elevated concentrations and toxicity of the drug result from the shunting of portal blood away from the liver, significantly reducing the degree of "first pass metabolism" for this drug, i.e. the amount of orally administered drug removed by the gut and liver during absorption.

7 Miscellaneous Conditions

a. Renal disease

Although renal impairment may be seen in patients with liver disease the available evidence suggests that renal disease per se does not alter the rate of metabolism of the majority of drugs that are mainly metabolised by the liver.

Thus Glogner, Lange & Pfab (1968) noted that the plasma tolbutamide half-life was normal in uraemic patients whilst Fabre et al (1967) noted/

noted that such patients did not develop any higher plasma phenobarbitone concentrations whilst receiving the drug than similarly treated volunteers. In addition, in uraemic patients, Prescott (1969) found the oxidation of phenacetin to be normal, Thomson et al (1973) the metabolism of lignocaine to be normal whilst Mellk et al (1970) found diphenylhydantoin metabolism to be faster in uraemic patients than non-uraemic controls.

However, in contradistinction to these oxidative processes, there is evidence that some phase II reactions are affected by uraemia. Thus Ogg, Toseland & Cameron (1968) have reported prolonged isoniazid and para-aminosalicylic acid half-lives in uraemic patients indicating that acetylation and glycine conjugated are slowed. However, the chloramphenicol half-life appears to be normal in uraemia (Glazko et al, 1949; McCurdy, 1963) suggesting that such patients have a normal rate of glucuronide formation. There is also some evidence to suggest that sulphate conjugation is also normal (Reidenberg, 1971).

a. Thyroid dysfunction

As might be expected, thyroid dysfunction affects drug metabolism. The plasma half-life of antipyrine is shortened in hyperthyroid patients and prolonged in hypothyroidism (Crooks et al, 1973).

b. Anaemia

There is conflicting evidence of the effect of iron deficiency anaemia per se on drug metabolism; Stevenson & O'Malley (1973) noting no change in the antipyrine half-life whilst Langman & Smithard (1977) noted the antipyrine clearance to be faster in anaemic patients.

SUMMARY

There are very many factors which determine the rate at which the liver metabolises any given drug. These include the number of functioning hepatocytes and the activity of the microsomal enzymes within each hepatocyte which can be affected by age, ethanol consumption diet and drug therapy. In addition, for drugs with certain physico-chemical properties liver blood flow is an important factor in determining its rate of metabolism. All these factors either singly or in combination can affect the rate of metabolism of drugs by the liver.

SECTION II

PARACETAMOL, ANTIPYRINE AND LIGNOCAINE METABOLISM IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE.

PARACETAMOL, ANTIPYRINE AND LIGNOCAINE METABOLISM IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE.

As has been discussed in the previous section there have been conflicting reports of the ability of patients with chronic liver disease to metabolise drugs at normal rates. Given the many factors influencing drug metabolism, however, this is perhaps not surprising. This study was therefore undertaken to compare the metabolism and elimination of three different drugs in patients with chronic liver disease with that of control subjects. The drugs investigated were paracetamol, antipyrine and lignocaine. They were administered consecutively over a short period as there has been no previous study comparing the elimination of different drugs in the same patients with chronic liver disease. Particular attention was given to the pathological and clinical status of the patients and to concurrent and previous drug therapy.

These three drugs were chosen because they have different physico-chemical and pharmacokinetic properties and different primary routes of metabolism. Antipyrine has previously been widely used to assess hepatic microsomal drug metabolising capacity, whilst the metabolism of paracetamol was of practical therapeutic interest as doubts have been expressed regarding the safety of this drug in patients with liver disease.

CHAPTER 1.

CHARACTERISTICS OF DRUGS STUDIED

PARACETAMOL

(A) GENERAL

Paracetamol (N-acetyl-p-aminophenol) is a weakly acidic drug with a pK_a of 9.5 and a molecular weight of 151.2. Although it has anti-pyretic and analgesic actions similar to aspirin (Beaver, 1966) it has only a weak anti-inflammatory action. In therapeutic doses it is a safe analgesic but in overdosage causes severe hepatic necrosis (Proudfoot and Wright, 1970; Prescott et al., 1971; Clark et al., 1973).

(B) ABSORPTION & DISTRIBUTION

Paracetamol is rapidly and essentially completely absorbed from the gastrointestinal tract; predominantly from the upper small intestine. Mean peak plasma concentrations after administration of paracetamol solution, tablets and capsules have been observed at 22 mins. (Nimmo et al., 1975), 1.4 hours (Heading et al., 1973) and 1 - 2 hours (Prescott et al., 1968) respectively. Its rate of absorption has been shown to be dependent on the rate of gastric emptying (Heading et al., 1973; Nimmo et al., 1975).

It is widely distributed throughout most body fluids and extensive tissue binding does not seem to occur (Koch-Weser, 1976). There is no significant binding of the drug to human plasma at therapeutic plasma concentrations (Gazzard et al., 1973). In normal subjects its volume of distribution has been noted to be 0.60 ± 0.07 l/Kg and its systemic bioavailability 0.89 ± 0.04 (Rawlins, Henderson and Hijab, 1977).

(C) METABOLISM

The drug is extensively metabolised in the liver although some metabolism may occur in gastro-intestinal mucosa (Josting, Winne and Bock, 1976). Its metabolic pathway is shown in Fig. 1. In normal subjects the plasma half-life has been shown to be 1.9 hours (Prescott et al., 1968), 1.95 hours (Nelson and Morioka, 1967) and 3.0 hours (Prescott et al., 1971).

Its hepatic extraction ratio has been estimated to be 0.10 (Chiou, 1975) and 0.2 (Clements and Prescott, 1976). It thus undergoes limited first pass metabolism and its rate of metabolism should be only moderately affected by changes in liver blood flow.

The drug is metabolised principally to the glucuronide (50%) and sulphate (25%) conjugates with only 3 - 4% of a therapeutic dose being excreted unchanged in the urine (Cummings, King and Martin, 1967; McGilvary et al., 1971). Minor metabolites are formed by further oxidation, hydroxylation and conjugation, their rate of formation being increased by inducers of drug metabolism and slowed by inhibitors (Mitchell et al., 1974).

The oxidative metabolite is a highly reactive arylating agent that is normally detoxified by preferential conjugation with hepatic glutathione and is subsequently excreted in the urine as conjugates with cysteine and mercapturic acid (Mitchell et al., 1974). These metabolites account for approximately 8% of the conjugates found in urine after therapeutic doses (Jagenberg, Nagy and Rodjer, 1968; Mitchell et al., 1974; Howie, Andriaessens & Prescott, 1977).

In overdosage, large amounts of the toxic intermediate metabolite are formed, and hepatic stores of glutathione are depleted. The free arylating metabolite then binds covalently to vital hepato-cellular macromolecules and thereby causes hepatic necrosis (Mitchell et al., 1973a;& b; Jollow et al., 1973; Potter et al., 1973).

(D) RENAL EXCRETION

Paracetamol glucuronide and sulphate are excreted by active tubular secretion since their overall renal clearance is higher than the glomerular filtration rate (Prescott and Wright, 1973). According to Milne (1965) the renal excretion of drugs with pK_a values of between 3.0 and 7.5 is pH dependent. As paracetamol has a pK_a of 9.5 changes in urine pH will therefore not influence its renal clearance. It has, however, been shown that the renal clearance of paracetamol depends on the urine flow rate (Prescott and Wright, 1973).

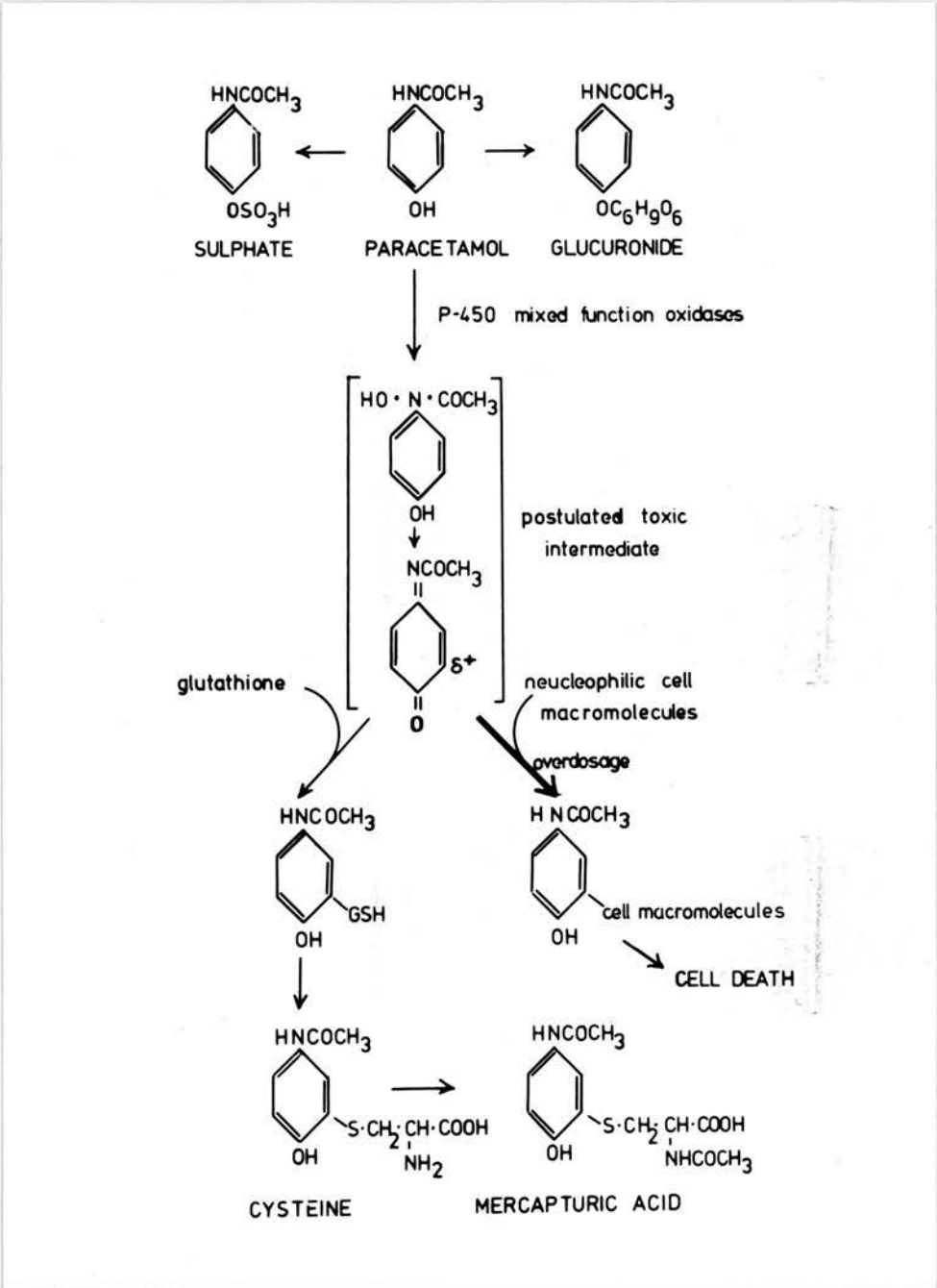

Fig. 1

A scheme of the metabolic pathway of paracetamol in man.

(Mitchell et al, 1974).

ANTYPYRINE

(A) GENERAL

Antipyrine (Phenazone) (Fig. 2) is a weak base with a pK_a of 1.4 and a molecular weight of 188.2. It was first introduced into medicine in the late 19th century as an antipyretic agent and was also subsequently used as an analgesic and anti-inflammatory agent. Its clinical use declined partly because of fears of toxicity and partly because it was thought not to be superior to other simple analgesics such as aspirin.

(B) ABSORPTION AND DISTRIBUTION

It is rapidly and essentially completely absorbed from the gastrointestinal tract; peak plasma concentrations being obtained in 1 - 2 hours (Woodbury and Fingle,1975a). It is rapidly distributed throughout total body water and was previously used to measure total body water (Soberman et al., 1949). It is less than 10% bound to plasma proteins. In normal subjects its volume of distribution has been noted to be 40.6 $\pm$ 8.0L (Stevenson, 1977).

(C) METABOLISM

It is extensively metabolised by cytochrome P-450 dependent liver microsomal enzymes, only 5% of the unchanged drug appearing in the urine (Brodie and Axelrod, 1950). 30 - 40% is converted to 4-hydroxyantipyrine which is then conjugated with glucuronic and sulphuric acids prior to urinary excretion. Two further primary metabolites - 3-hydroxymethyl and 3-carboxyantipyrine have also/

also been demonstrated (Yochimura, Shimeno and Tsukamoto, 1968). Some of the durg may also be converted to norphenazone with loss of the methyl group in the 2 position (Baty and Price Evans, 1973).

The assumption that the half-life of antipyrine provided a valid measure of its rate of metabolism has been justified by the demonstration of a correlation between the plasma disappearance of antipyrine and the appearance of 4-hydroxyantipyrine in urine (Huffman, Shoeman and Azarnoff, 1974). The drug is also excreted in saliva, where its half-life has been shown to be similar to that in plasma (Welch et al., 1975).

It has a low hepatic extraction ratio (0.04) (Rane, Wilkinson and Shand, 1977). There is no appreciable first-pass effect and because it has a sufficiently low hepatic clearance its elimination is not greatly influenced by hepatic blood flow (Branch et al., 1974).

In healthy volunteers its plasma half-life has been shown to be 10.9 $\pm$ 1.9 hours (S.D.) (Vessell and Page, 1968a), 12.0 $\pm$ 3.5 hours (O'Malley et al., 1971), 13.1 $\pm$ 7.5 hours (Kolmodin, Azarnoff and Sjoqvist, 1969), and 13.8 $\pm$ 5.6 hours (Vestal et al., 1975).

Because it is rapidly absorbed and extensively metabolised by the liver, antipyrine has been widely used as a general index of liver microsomal drug metabolising capacity. This, however, may not be a valid concept as intra-individual variation is considerable and in healthy subjects there is often a poor correlation with the plasma half-lives of other drugs in the same subjects. (Vessell and Page, 1968b; Davies and Thorgiersson, 1971; Kadar et al., 1973) and with other possible indices of microsomal drug metabolising enzyme activity e.g. urinary excretion of 6-B-hydroxycortisol or D-glucaric acid (Smith and Rawlins, 1974). On the other hand/

hand, a good correlation has been demonstrated in the same patients between the "in vivo" antipyrine half-life and cytochrome P-450 activity (Sontaniemi et al., 1977), whilst Smith and Rawlins (1974) demonstrated a correlation between the antipyrine and phenylbutazone half-lives.

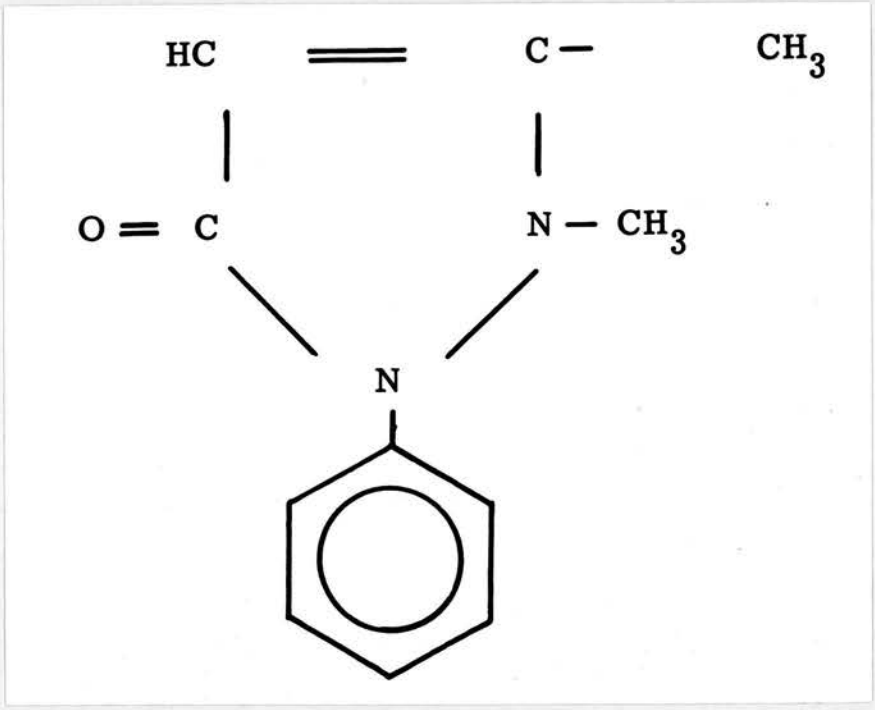

Fig. 2

The structure of antipyrine.

LIGNOCAINE

(A) GENERAL

Lignocaine (diethylglycylxylidide) is an organic base with a pK_a value of 7.85 (Eriksson, 1966) and a molecular weight of 243.3. The drug has a number of other actions in addition to its blocking action on peripheral nerves (Benowitz and Meister, 1978). It produces a variety of central nervous system symptoms such as dizziness, lightheadedness, tremor, convulsions, confusion and numbness of the tongue and lips (Foldes et al., 1960; Foldes et al., 1965; Eriksson and Persson, 1966; Boyes and Keenaghan, 1971) and its effective in the treatment of ventricular arrhythmias after acute myocardial infarction (Gianelly et al., 1967; Jewitt et al., 1968).

(B) ABSORPTION AND DISTRIBUTION

It is rapidly absorbed from the gastrointestinal tract, peak levels occuring 30 - 60 minutes after oral administration (Scott, 1971; Boyes and Kennaghan, 1971; Adjepon-Yamoah, 1973). In keeping with other lipid soluble drugs, it has a large volume of distribution and when fully distributed only 6% of the total amount in the body is present in the blood (Thomson et al., 1973). In healthy volunteers the steady state volume of distribution was noted to be 0.65 $\pm$ 0.17 L/Kg (Nation, Triggs and Selig, 1977). Thus, although it is 66% bound to plasma proteins (Eriksson, 1966) any change in plasma protein binding will have little effect on the concentration of the pharmacologically active unbound drug.

The drug has a high hepatic extraction ratio: estimated to be 0.6 (Seldon and Sasahara, 1967), 0.7 (Stenson, Constantino and Harrison, 1969) and 0.8 (Rane, Wilkinson and Shand, 1977) so that clearance of the drug, which is principally by hepatic metabolism, is highly dependent on liver blood flow. Because of its high hepatic extraction ratio it undergoes extensive first pass metabolism. Following an oral dose a large percentage of the drug is removed during passage through the liver in the portal circulation; only about 35% reaching the systemic circulation (Boyes and Kennaghan, 1971).

(C) METABOLISM

The probable sequence of lignocaine metabolism in man is shown in Fig. 3 (Adjepon-Yamoah, 1973). Lignocaine is first de-ethylated to ethylglycylxylidide (EGX). Most of the EGX then probably undergoes rapid amide hydrolysis to form 2, 6-xylidine (Hollunger, 1960b) which, in turn, is hydroxylated to form 4-hydroxyxylidine. EGX is also partly slowly de-ethylated to form glycylxylidide (GX), which is probably not extensively metabolised as it has a long biological half-life. 4-hydroxyxylidine could be formed partly from lignocaine, EGX or GX by hydroxylation.

Lignocaine is probably metabolised mainly by the liver (Akerman et al., 1966; Stenson, Constantino and Harrison, 1969; Boyes et al., 1971). In healthy volunteers the plasma half-life has been shown to be 1.4 hours (Adjepon-Yamoah, Nimmo and Prescott, 1974), 1.5 hours (Boyes et al., 1971) and 1.8 hours (Thomson et al., 1973).

In the rabbit is metabolised by hepatic microsomal enzymes (Hollunger 1960a, b, c) and the same system is probably responsible for the biotransformation of the drug in man.

Drugs that induce (phenobarbitone) and inhibit (SKF-525) hepatic microsomal enzymes have been shown to enhance or impair, respectively, lignocaine metabolism in animals (Di Fazio and Brown, 1972; Lautt and Skelton, 1977). It is possible that lignocaine is metabolised at other sites such as the gut wall and the kidneys (Åkerman et al., 1966; Åström, 1971).

(D) RENAL EXCRETION

Only 1 - 2% of a dose of lignocaine is normally excreted unchanged in the urine; excretion being virtually complete by 12 hours. EGX is not detected in urine after 36 hours whilst the amount of GX excreted in the urine gradually increases with time and it is still present at 48 hours (Adjepon-Yamoah, 1973). The renal clearance of lignocaine is higher in acidic urine but is not significantly affected by urine flow rate (Eriksson and Granberg, 1965). Changes in urine pH have no significant effect on the plasma half-life of lignocaine.

Table II compares the various characteristics of the 3 drugs studied. The figures for plasma protein binding, volumes of distribution, plasma clearance and plasma half-lives are from young healthy subjects.

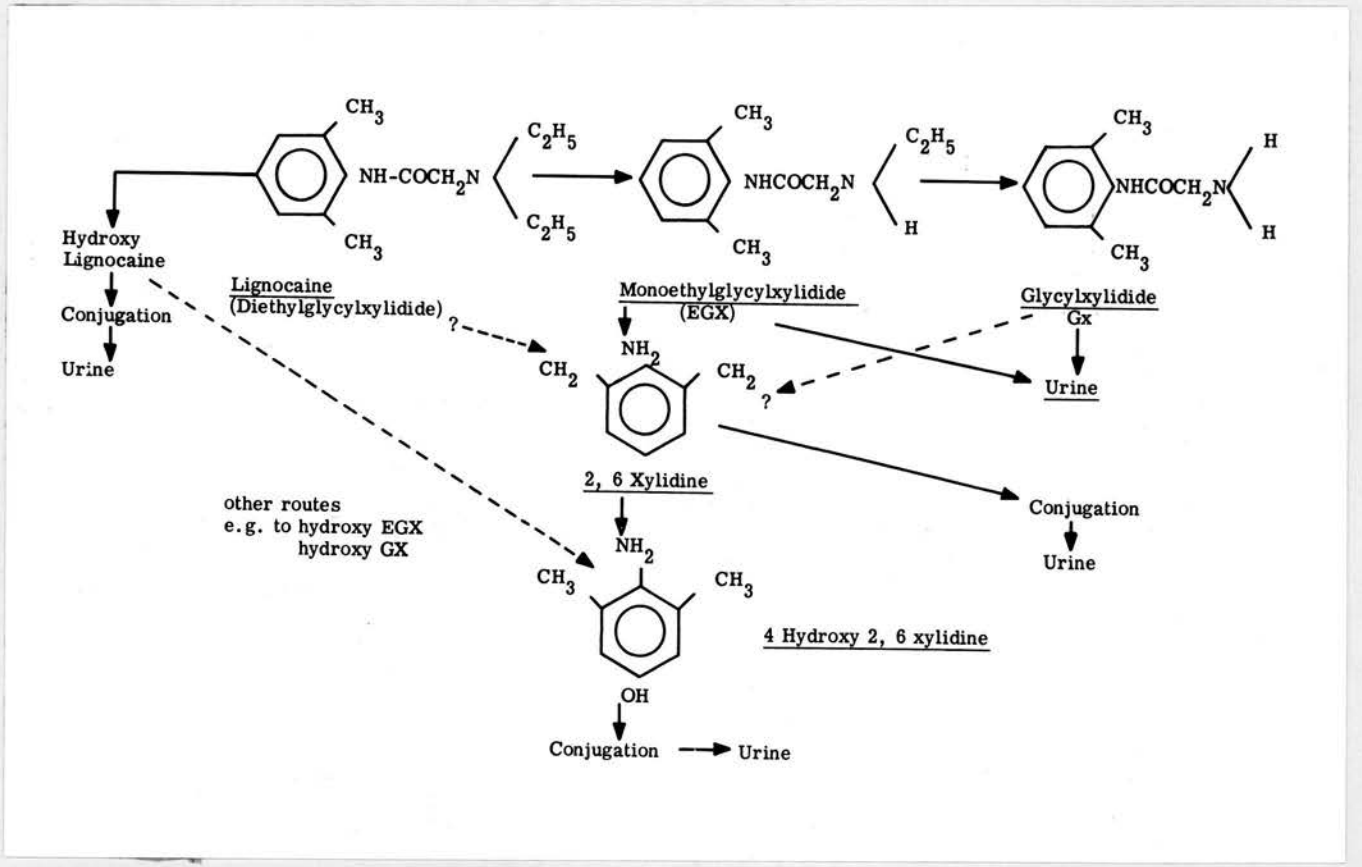

Fig. 3

A scheme of the metabolic pathway of lignocaine in man (Adjepon-Yamoah, 1973). The arrows indicate the proposed sequence of formation of the lignocaine metabolites.

TABLE II

CHARACTERISTICS OF DRUGS STUDIED

	Major route of metabolism	PK_a	Mol. Wt.	Hepatic extraction ratio	Systemic bioavailability (%)	Plasma protein* binding (%)	Volume of* distribution	Plasma clearance* ml/min.	Plasma* Half-life (hours)
Paracetamol	conjugation	9.5	151.2	0.10 - 0.20	89	0 - 5	0.60 l/kg	352 ± 40 ml/min	1.9 - 2.0
Antipyrine	hydroxylation	1.4	188.2	0.04	100	< 10	40.6 ± 8.0 l	40 ± 8 ml/min	10.9 - 13.8
Lignocaine	N- dealkylation	7.85	243.3	0.6 - 0.8	35	66	0.65 ± 0.17 l/kg	700 - 800 ml/min	1.4 - 1.8

*Figures from young healthy subjects

CHAPTER 2.

ANALYTICAL METHODS

(A) PARACETAMOL

1. Plasma paracetamol and conjugates

Plasma paracetamol and its sulphate and glucuronide conjugates were measured by high performance liquid chromatography (Ariaenssens and Prescott, 1978).

Aliquots of plasma were pipetted into glass tubes which were placed on a vortex mixer while internal standard/protein precipitant solution was added slowly. The latter contained N-propionyl-4-aminophenol in aqueous perchloric acid. The tubes were centrifuged and up to 5µl of the clear supernatant injected directly onto the column.

An Orlita pump (Model AE 10-4) was used with a Waters model 440 U.V. absorbance detector (254 mm filter) and peak areas were measured with a Hewlett-Packard HP 3370A integrator. The columns (stainless steel tubes 100 mm x 4.9 mm i.d.) were slurry packed with octadecylsilane - bonded spherical silica, 5 µm diameter and fitted with a septum injector. The solvent was 0.1 M potassium dihydrogen phosphate, 98% formic acid and isopropanol (100:0.1: 1.7 V/V/V), and the flow rate was 0.9 ml/min.

The limit of measurement with a 5 µl injection was less than 1 µg/ml for all compounds. The standard deviation of replicate assays of paracetamol and its glucuronide and sulphate conjugates was less than 3% (mean 1%) for each compound with concentrations ranging from 1 - 250 µg/ml (paracetamol equivalent). The day to day reproducibility was 3 - 4%.

2. Urinary paracetamol and metabolites

Paracetamol and its sulphate, glucuronide, cysteine and mercapturic acid conjugates in urine were estimated by a modification of the high performance liquid chromatography method of Howie et al., (1977).

Internal standard solution (N-propionyl-p-aminophenol) was added to urine and after mixing, 2 - 4 µl was injected onto the column. Aqueous paracetamol standards were run with each set of unknowns.

The apparatus was as described previously except that a Cecil Model 212 ultraviolet detector (242nm) was used with a Honeywell Model 194 recorder. The column was an internally polished stainless steel tube, 170 x 4.9 mm i.d., packed with octadecylsilane-bonded spherical silica, particle size 5 µm with a septum injector. The solvent was isopropanol: 1% acetic acid (1:99 V.V.) with a flow rate of 1.6 ml/min.

At concentrations of 1000, 200, 50 and 10 µg/ml the standard deviations of the assay were 1,2,4 and 9% respectively for paracetamol and the conjugates.

(B) ANTIPYRINE

Antipyrine in plasma was estimated either by gas-liquid chromatography (Prescott et al., 1973) or by high performance liquid chromatography (Adriaenssens and Prescott, unpublished).

1. Gas-liquid chromatography method

Plasma was made alkaline with NaOH and extracted into chloroform containing phenacetin as internal standard. The tubes were shaken mechanically for 10 min, centrifuged, and the upper aqueous phase and interface removed by aspiration. The chloroform extract was decanted and removed by placing the tubes in a water bath at 90°. The residue was dissolved in chloroform and aliquots injected into the gas chromatograph.

A Hewlett-Packard Model 402 gas chromatograph was used with a 6ft x $\frac{1}{4}$in. o.d. gas "U" tube column packed with 80/100 mesh Gas-Chrom Q coated with 0.5% SE 30 plus 0.5% Carbowax 20 M run at 220°C.

The recovery of antipyrine from aqueous solutions and plasma was the same and the mean standard deviation of the method for human plasma samples containing 10 - 50 µg/ml was 2.8%.

2. High performance liquid chromatography method

Perchloric acid and 4-amidopyrine as internal standard were added to plasma samples. The tubes were centrifuged, the clear supernatant transferred to another tube and triethylamine added. After mixing, aliquots were injected directly onto the column.

The apparatus and column used was as described for the assay of paracetamol in plasma (page38) and the solvent was water, isopropanol and triethylamine 100:10:.07.V/V/V (pH 11.0) at a flow/

flow of 0.8 ml/min. The antipyrine and amidopyrine eluted in 3.5 and 4.8 mins respectively.

The standard deviation for replicate analyses for plasma containing 5 - 50 µg/ml was 4.3% and the day to day reproducibility was 4.4%.

COMPARISON OF GLC AND HPLC METHODS

21 plasma samples from 5 patients were assayed by both GLC and HPLC. The correlation coefficient "r" was 0.98 (Fig. 4). The mean percentage difference of the HPLC method over the GLC method was 5.53 $\pm$ 1.06.

A comparison of the antipyrine plasma half-lives obtained by the two methods in the 5 patients is shown in Table III

There was no significant difference between the half-life values obtained by the two methods ($P > 0.3$).

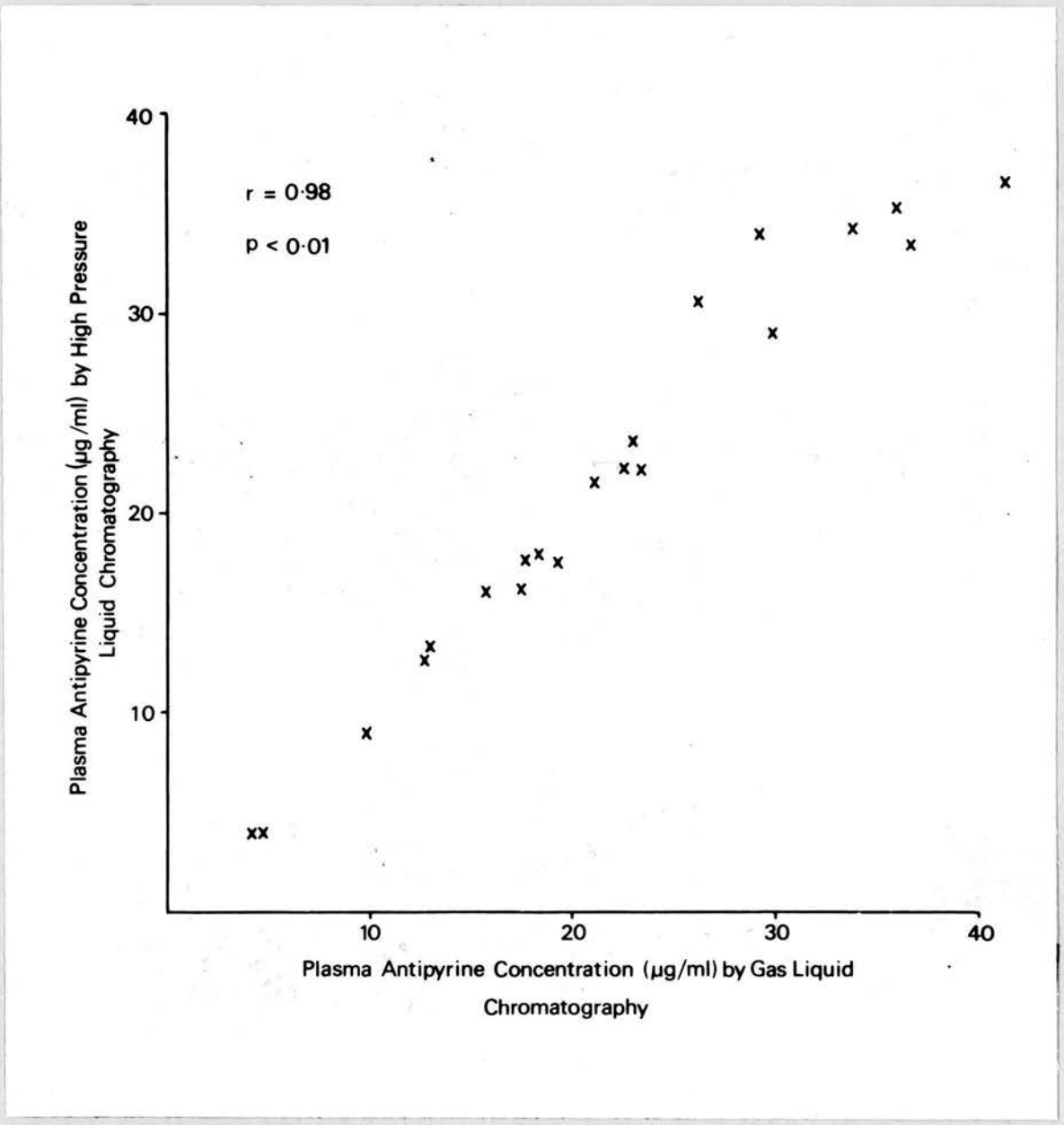

Fig. 4

Correlation between the plasma antipyrine concentration as estimated by gas-liquid chromatography and high performance liquid chromatography.

TABLE III

PLASMA ANTIPYRINE HALF-LIFE VALUES IN 5 PATIENTS FOLLOWING AN ORAL DOSE OF ANTIPYRINE (18mg/kg) AS ESTIMATED BY GLC AND HPLC

	Antipyrine half-life (Hours)		% change in half-life relative to GLC value
Patient No.	GLC	HPLC	
1	26.0	24.1	- 7.3
2	65.8	60.8	- 7.6
3	9.0	9.4	+ 4.4
4	8.3	8.4	+ 1.2
5	17.0	16.1	- 5.3
Mean	25.2	23.8	5.2
S.D.	23.8	21.6	2.6

(C) LIGNOCAINE

Lignocaine and its metabolites, ethylglycylxylidide (EGX), glycylxylidide (GX) and 4-hydroxyxylidine were estimated in plasma and urine by gas-liquid chromatography (Adjepon-Yomoah and Prescott, 1974).

ESTIMATION OF LIGNOCAINE, EGX & GX IN PLASMA & URINE

Plasma and urine samples (2ml) were made alkaline with NaOH and extracted with redistilled dichloromethane (5ml) containing aceto-p-toluidide (APT) (0.125 to 2.5 µg/ml) as the internal standard. The tubes were centrifuged and the dichloromethane extract decanted into another tube. Acetic anhydride (10 µl) and anhydrous pyridine (2 µl) were added and the contents evaporated to dryness. The residue was dissolved in ethanol (20 µl) and aliquots (1-4 µl) were injected into the gas chromatograph.

A Hewlett Packard Model 5750 chromatograph fitted with a Model 15161A nitrogen sensitive flame ionization detector was used with a Moseley model 7128A strip chart recorder. The column was a 4ft x $\frac{1}{4}$ inch o.d. U-shaped glass tube packed with 3% cyclohexane dimethanolsuccinate on 100/120 mesh Gas-chrom Q. The column temperature was 200^{o} rising to 245^{o} at 3^{o} per min. after an initial delay of 2 min.

The concentrations of lignocaine, EGX, or GX to APT were calculated from the peak height ratios relative to standards run at the same time. The limits of detection for lignocaine, EGX and GX added to plasma were approximately 0.01, 0.01 and 0.03 µg/ml respectively. The standard deviation of replicate assays of lignocaine, EGX and GX in plasma was 3.4, 6.0 and 7.7% and in urine 3.1, 3.6 and 6.3% respectively.

ESTIMATION OF CONJUGATED 4-HYDROXYXYLIDINE IN URINE

Sodium metabisulphate (1mg), about 10mg sodium acetate buffer and glusulase (0.05ml) (a mixture of glucuronidase and sulphatase) were added to urine (1ml) and the mixture incubated at 40° for 45 min.

After rapid cooling to 0°C phosphate buffer (pH 10.7) (0.12ml) was added and the pH of the solution was adjusted to 7.2 with NaOH. Freshly redistilled dichloromethane (5ml) containing 5 µg/ml N-butyryl-p-aminophenol (NBA) as the internal standard was added and the tubes shaken and centrifuged. The upper aqueous phase was transferred to another tube and re-extracted with a further volume of dichloromethane (3ml). After centrifugation, the organic extracts were combined and acetic anhydride (60 µl) and anhydrous pyridine (5 µl) added and mixed. The tubes were incubated at 45°C for 40 min. and evaporated to dryness. The residue was dissolved in ethanol (20 µl) and samples chromatographed (1-4 µl).

A Hewlett-Packard Model 402 chromatograph equipped with a standard flame ionization detector was used. The column was a 4ft x $\frac{1}{4}$ inch o.d. U-shaped glass tube packed with 1% Carbowax 20M on 80/100 mesh Gas-chrom Q at 205°C.

The concentrations of total 4-OH-xylidine were calculated from the peak height ratios relative to standards run simultaneously.

CHAPTER 3.

PARACETAMOL, ANTIPYRINE AND LIGNOCAINE METABOLISM IN HEALTHY SUBJECTS

In order that meaningful comparisons could be made between the metabolism and excretion of paracetamol, antipyrine and lignocaine in patients with chronic liver disease and healthy subjects, the metabolism and excretion of these drugs was first studied in healthy subjects.

OUTLINE OF STUDIES

The healthy subjects used in the studies, were technical or medical staff. None had a past history of significant illnesses, especially jaundice, and all were entirely well at the times the 3 studies were carried out. None had been taking any regular medications prior to the studies being performed or took any on the days of the studies. In all the subjects the 3 studies were carried out at least 4 days apart and were usually completed within 4 weeks. All 3 studies followed a similar basic pattern. After an 11 hour overnight fast the drug was administered at 0900. Fluid and food were withheld for 2 and 4 hours respectively after drug ingestion. After these times no restriction was placed on fluid or food intake. Smoking was not permitted for the first 4 hours of the study whilst alcohol was not permitted for the duration of each test. The subjects were ambulant during all periods of the tests; no restrictions being placed on their activity.

Following withdrawal of venous blood the plasma was separated and then stored at -20°C within 2 - 3 hours. For each collection of urine the urine volume and pH was noted and an aliquot stored within 2 - 3 hours at -20°C.

A. Paracetamol

Paracetamol metabolism and excretion was studied in 8 healthy male subjects aged 21 - 34 years (mean 29 years) with weights ranging from 63 to 75 kg (mean 67 kg). Following the overnight fast three tablets of paracetamol ("Panadol") each of 500mg were taken with 50ml of water. Venous blood (10ml in lithium heparin tubes) was withdrawn from an antecubital vein at 0, 3, 5, 7 and 9 hours after ingestion. All urine was collected for 24 hours from time zero.

B. Antipyrine

Antipyrine metabolism was studied in 10 healthy male subjects aged 28 - 38 years (mean 31 years) with weights ranging from 54 to 76kg (mean 68 kg). Following the overnight fast antipyrine powder in a dose of 18mg/kg was taken dissolved in 50ml of dilute orange juice. Venous blood (10ml in lithium heparin tubes) was withdrawn from an antecubital vein at 0, 4, 8, 12 and 24 hours after ingestion.

C. Lignocaine

Lignocaine metabolism and excretion was studied in 8 healthy male subjects aged 26 - 34 years (mean 30 years) with weights ranging from 61 to 76 kg (mean 69 kg). Following the overnight fast 400 mg of lignocaine (as lignocaine hydrochloride powder: "Xylotox") was taken dissolved in 50ml of dilute orange juice. Venous blood (10ml in lithium heparin tubes) was withdrawn from an antecubital vein at 0, 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours after ingestion.

Plasma half-life

For all three drugs the plasma half-lives were calculated from the linear regression of the logarithms of the plasma concentrations against time by using the method of least squares.

Volume of distribution

The volume of distribution (V_D) of antipyrine was calculated from the equation

$$V_D = \frac{\text{Dose}}{\text{Plasma concentration at zero time}}$$

The plasma concentration at zero time was derived by extrapolating the plasma concentrations at the different sampling times to time zero.

Plasma clearance

The plasma clearance of antipyrine was calculated from the equation

$$\text{clearance} = \frac{0.693 \times V_D}{\text{plasma half-life}}$$

Statistical Methods

The statistical methods used in the analysis of all data were either Student's 't' test (2 tail test) for paired and unpaired data and the coefficient of correlation ('r') for correlations between sets of data.

Standard Deviation

Unless otherwise stated standard deviations have been used throughout the thesis.

A. PARACETAMOL METABOLISM AND EXCRETION

1. Results:

a. Plasma

The plasma concentrations of paracetamol and its glucuronide and sulphate metabolites at the different sampling times, are shown in Tables IV, V and VI.

In all subjects the highest plasma paracetamol concentration was seen in the 3 hour sample; the concentrations ranging from 10.2 to 15.0 µg/ml (mean 12.9 µg/ml). Nine hours after ingestion the plasma concentration ranged from 1.8 to 3.1 µg/ml (mean 2.3 µg/ml). There was no correlation between the 3 hour plasma paracetamol concentration and the subject's weight ($r = 0.22$; $p > 0.01$).

The plasma paracetamol half-life (Table IV) ranged from 2.06 to 2.6 hours with a mean of 2.4 hours. There was no correlation between the plasma paracetamol half-life and the subject's weight, ($r = 0.28$; $p > 0.1$).

In all 8 subjects the highest plasma concentrations of both the glucuronide and sulphate metabolites were seen in the 3 hour sample. With regard to plasma glucuronide the plasma concentrations at 3 hours ranged from 9.5 to 18.3 µg/ml (mean 14.3 µg/ml) falling to 3.4 to 6.8 µg/ml (mean 4.9 µg/ml) at 9 hours. The paracetamol sulphate concentrations at 3 and 9 hours were 3.2 to 7.8 µg/ml (mean 4.7 µg/ml) and 0.6 to 2.2 µg/ml (mean 1.5 µg/ml respectively).

The mean paracetamol to glucuronide and paracetamol to sulphate ratios at 3 hours were 0.90 and 2.73; at 5 hours 0.60 and 1.94; at 7 hours 0.51 and 1.71 and at 9 hours 0.47 and 1.61 respectively.

TABLE IV

PLASMA PARACETAMOL CONCENTRATIONS (µg/ml) AND HALF-LIFE VALUES (HOURS) IN HEALTHY SUBJECTS FOLLOWING 1500 mg OF PARACETAMOL ORALLY

SUBJECT NO.	AGE (yrs.)	Wt (kg)	HOURS AFTER INGESTION 3	5	7	9	HALF-LIFE (hours)
1	28	65	12.3	6.2	2.9	2.0	2.26
2	34	63	15.0	9.2	5.1	3.1	2.62
3	29	67	14.5	8.8	5.3	3.0	2.62
4	31	65	11.0	6.1	3.7	2.1	2.52
5	26	69	15.5	6.4	3.7	2.0	2.06
6	21	63	14.4	7.9	4.4	2.6	2.42
7	34	70	10.4	5.4	3.0	2.0	2.52
8	26	70	10.2	6.0	3.1	1.8	2.41
MEAN	28.6	66.5	12.9	7.0	3.9	2.3	2.43
S.D.	4.4	2.9	2.2	1.4	0.9	0.5	0.19

TABLE V

PLASMA PARACETAMOL GLUCURONIDE CONCENTRATIONS (µg/ml) IN HEALTHY SUBJECTS FOLLOWING 1500 mg. OF PARACETAMOL ORALLY

	HOURS AFTER INGESTION			
SUBJECT NO.	3	5	7	9
1	18.3	15.0	8.7	5.8
2	13.4	11.6	7.0	4.8
3	9.5	7.4	5.5	3.5
4	17.6	14.3	10.6	6.3
5	15.7	13.7	10.5	6.8
6	12.0	10.0	7.0	4.7
7	11.0	8.7	5.4	3.4
8	16.9	11.9	6.6	4.2
MEAN	14.3	11.6	7.7	4.9
S.D.	3.3	2.7	2.1	1.3

TABLE VI

PLASMA PARACETAMOL SULPHATE CONCENTRATIONS (µg/ml) IN HEALTHY SUBJECTS FOLLOWING 1500 mg. OF PARACETAMOL ORALLY

	HOURS AFTER INGESTION			
SUBJECT NO.	3	5	7	9
1	6.2	5.0	3.4	2.1
2	5.7	5.2	2.8	2.2
3	4.1	2.9	2.6	1.8
4	2.3	2.0	1.2	0.6
5	4.7	3.5	2.7	1.7
6	7.8	5.0	3.2	2.0
7	3.7	3.0	1.4	0.7
8	3.2	2.3	1.0	0.6
MEAN	4.7	3.6	2.3	1.5
S.D.	1.8	1.3	0.9	0.7

b. Urine

The 24 hour urine volumes and the total amounts of unchanged paracetamol and its sulphate, glucuronide, mercapturate and cysteine conjugates excreted by each of the normal subjects are shown in Table VII. The total recovery ranged from 86.5 to 99.7% (mean 92%) and there was no correlation between the total amount excreted and the subject's urine volume ($r = 0.05$; $p > 0.1$). There was also no correlation between the amount of unchanged paracetamol excreted and the subject's urine volume ($r = 0.66$; $p > 0.05$).

When the excretion of paracetamol and its metabolites are expressed as a percentage of the ingested dose the following results are obtained (mean $\pm$ S.D.)

paracetamol	3.3 $\pm$ 1.2
sulphate	31.0 $\pm$ 7.3
glucuronide	50.0 $\pm$ 9.9
mercapturate	4.4 $\pm$ 1.5
cysteine	3.5 $\pm$ 0.9

TABLE VII

24-HOUR EXCRETION OF UNCHANGED PARACETAMOL AND ITS GLUCURONIDE, SULPHATE, MERCAPTURATE AND CYSTEINE METABOLITES (mg.) IN HEALTHY SUBJECTS FOLLOWING 1500mg OF PARACETAMOL ORALLY

SUBJECT NO.	UNCHANGED PARACETAMOL	PARACETAMOL GLUCURONIDE	PARACETAMOL SULPHATE	PARACETAMOL MERCAPTURATE CONJUGATE	PARACETAMOL CYSTEINE CONJUGATE	TOTAL EXCRETION (mg)	% RECOVERY	URINE VOLUME
1	36.6	790	536	80.2	52.6	1495	99.7	840
2	72.8	666	546	32.3	29.9	1347	89.8	1940
3	68.7	555	525	89.4	59.4	1298	86.5	1325
4	42.3	978	255	79.2	65.0	1420	94.7	1600
5	24.8	878	385	51.4	44.8	1384	92.3	585
6	62.6	577	551	92.1	61.7	1344	89.6	930
7	53.9	723	504	44.4	67.0	1392	92.8	1145
8	37.1	843	366	63.9	40.7	1351	90.1	940
MEAN	49.9	751	459	66.6	52.6	1379	91.9	1163
S.D.	17.3	149	110	22.1	13.1	59.7	4.0	441

2. DISCUSSION

The mean paracetamol half-life in this group of healthy subjects of 2.4 ± 0.2 hours is slightly longer than the mean values of 1.95 ± 0.2, 2.0 ± 0.5 and 2.0 ± 0.4 hours previously reported in healthy subjects (Nelson and Morioka, 1963; Prescott et al 1968; Prescott et al, 1971).

The urinary excretion of paracetamol and its metabolites expressed as a percentage of the ingested dose is similar to those reported in other studies in normal subjects (Cummings et al., 1967; Jagenburg et al., 1968; McGilvary et al., 1971; Levy and Yamada, 1971; Mitchell et al., 1973).

In this study the correlation between the excretion of unchanged paracetamol and the 24 hour urine volume just failed to reach statistical significance, although Prescott & Wright (1973) have demonstrated that the renal clearance of paracetamol depends on the urine flow rate.

B. Antipyrine Metabolism

1. Results:

The plasma concentrations of antipyrine at the different sampling times and the plasma half-life values and plasma clearance for each subject are shown in Table VIII. In all subjects the highest plasma antipyrine concentrations were seen in the 4 hour sample where the concentrations ranged from 19.2 to 25.3 µg/ml (mean 22.3 µg/ml). At 24 hours the plasma concentrations ranged from 4.5 to 9.9 µg/ml (mean 6.5 µg/ml). There was no correlation between the subject's weight and their 4 hour antipyrine concentration ($r = 0.15$; $p > 0.1$).

The individual plasma half-life values ranged from 8.4 to 17.0 hours (mean 11.6 hours). There was no correlation between the subject's weight and their plasma antipyrine half-life ($r = 0.14$; $p > 0.1$).

The individual plasma clearances ranged from 33.7 to 51.5 mls/min (mean 43.8 ml/min) and the volume of distribution from 37.01 to 49.6 litres (mean 43.2 $\pm$ 7.71 litres).

TABLE VIII

PLASMA ANTIPYRINE CONCENTRATIONS (µg/ml), HALF-LIFE VALUES (HOURS) AND PLASMA CLEARANCE (ml/min) IN HEALTHY SUBJECTS FOLLOWING ANTIPYRINE (18mg/kg) ORALLY

SUBJECT NO.	AGE (yrs.)	Wt (kg)	HOURS AFTER INGESTION 4	8	12	24	HALF-LIFE (hours)	PLASMA CLEARANCE (ml/min)
1	34	70	23.0	17.4	12.8	5.0	9.0	51.3
2	29	62	23.4	17.7	12.7	4.5	8.3	46.3
3	28	73	22.5	19.1	16.2	9.9	17.0	33.8
4	33	69	21.9	17.2	15.9	7.5	12.6	41.3
5	29	76	22.9	18.0	14.7	7.6	12.6	44.0
6	28	65	21.4	16.6	12.2	6.0	10.8	46.2
7	30	75	19.2	15.4	12.4	7.2	14.5	47.2
8	34	63	22.7	17.5	14.1	6.6	11.1	40.5
9	28	74	25.3	18.7	13.1	4.9	8.4	51.3
10	38	54	21.0	15.8	13.1	6.3	11.6	37.0
MEAN	31.1	68.1	22.3	17.3	13.7	6.6	11.6	43.8
S.D.	3.5	7.0	1.6	1.2	1.4	1.6	2.8	6.1

2. DISCUSSION

The mean plasma antipyrine half-life (11.6 ± 2.8 hours) in this group of healthy subjects is similar to those reported by other workers in healthy subjects viz:- (mean ± S.D.)

10.9 ± 1.9 hours (Vessel & Page, 1968a; mean age of subjects 36 years)

13.1 ± 7.5 hours (Kolmodin et al., 1969)

12.0 ± 3.5 hours (O'Malley et al., 1971; mean age of subjects 26 years)

12.7 ± 4.3 hours (Vestal et al., 1975; mean age of subjects 33 years)

13.8 ± 5.8 hours (Vestal et al., 1975; mean age of subjects 50 years)

12.0 ± 6.4 hours (Branch, James and Read, 1973; age range of subjects 28 - 40 years).

The plasma clearance of antipyrine (43.8 ± 6.1 ml/min) in this study is similar to that reported in healthy subjects by Branch, James & Read (1976a) of 38.4 ± 10.8 ml/min and Stevenson (1977) of 40.0 ± 8.3 ml/min although less than the 58.6 ± 16.6 ml/min reported by Andreasen et al (1974).

The volume of distribution of antipyrine in this study (43.2 ± 7.7 litres) is similar to that found by Andreasen et al (1974) (36.9 ± 9.3 litres), Branch James & Read (1976a) (33.3 ± 6.9 litres) and Stevenson (1977) (40.6 ± 8.0 litres) in healthy subjects.

C. LIGNOCAINE METABOLISM

1. Results

a. Lignocaine

The plasma concentrations of lignocaine at the different sampling times and the plasma half-life values for each subject are shown in Table IX. In all 5 subjects in whom a 1 hour sample was taken, peak plasma lignocaine concentrations occurred at that time. Two hours after ingestion the mean plasma concentration was 0.44 µg/ml (range 0.21 to 0.67 µg/ml). Five of the subjects had no detectable amounts of lignocaine in the plasma 12 hours after ingestion; no subject having detectable lignocaine in the plasma at 24 hours (lower limit of detection of assay 0.01 µg/ml). There was no correlation between the subject's weight and the 1 or 2 hour plasma lignocaine concentrations ($r = 0.18$; $p > 0.1$).

The individual plasma half-life values ranged from 1.37 to 2.11 hours (mean 1.74 hours), and there was no correlation between the body weight and the plasma half-life ($r = 0.19$; $p > 0.1$).

TABLE IX

PLASMA LIGNOCAINE CONCENTRATIONS (µg/ml) AND HALF-LIFE VALUES (HOURS) IN HEALTHY SUBJECTS FOLLOWING 400 mg. OF LIGNOCAINE ORALLY

			HOURS AFTER INGESTION										
SUBJECT NO.	AGE (yrs)	Wt (kg)	1	2	3	4	5	6	8	10	12	24	HALF-LIFE (hours)
1	33	69	0.43	0.33	0.15	0.11	0.084	0.063	0.028	0.018	0	0	2.08
2	34	70	0.57	0.44	0.25	0.15	0.082	0.083	0.050	0.021	0.013	0	1.55
3	27	70	0.43	0.25	0.18	0.17	0.082	0.074	0.035	0.013	0	0	1.98
4	28	65	0.93	0.52	-	0.17	0.120	0.066	0.027	0.013	0	0	1.37
5	29	76	0.64	0.46	0.25	0.18	0.110	0.059	0.029	-	0	0	1.51
6	34	63	-	0.67	-	0.35	-	0.200	0.091	-	0.048	0	2.11
7	30	75	-	0.62	-	0.24	-	0.104	0.046	0.032	0.014	0	1.68
8	26	61	-	0.21	-	0.06	-	0.015	-	0.011	0	0	1.67
MEAN	30:1	68:6	0.60	0.44	0.21	0.18	0.096	0.083	0.044	0.018	0.01	0	1.74
S.D.	3.2	5.4	0.21	0.17	0.05	0.09	0.018	0.054	0.023	0.008	0.02	-	0.28

b. EGX

The plasma concentrations of EGX at the different sampling times and the apparent plasma half-life values for each subject are shown in Table X. Of the 5 subjects in whom a 1 hour plasma sample was taken the peak plasma EGX concentration was at 1 hour in 3 subjects and at 2 hours in the other two. Two hours after ingestion the mean plasma EGX concentration was 0.75 µg/ml (range 0.46 to 1.27 µg/ml). Only one subject (no. 8) had no detectable amounts of EGX 10 and 12 hours after ingestion (lower limit of detection of assay 0.01 µg/ml). At 24 hours only 1 subject had a detectable amount of EGX in the plasma.

The mean apparent half-life of EGX was 2.16 hours (range 1.26 to 3.85 hours).

There was no significant correlations between either the plasma lignocaine and EGX half-lives ($r = 0.45$; $p > 0.1$) or between the 1 or 2 hour plasma lignocaine concentrations and the EGX half-life ($r = 0.63$; $p > 0.05$ and $r = 0.51$; $p > 0.1$).

TABLE X

PLASMA CONCENTRATIONS OF EGX (µg/ml) AND APPARENT HALF-LIFE VALUES (HOURS) IN HEALTHY SUBJECTS FOLLOWING 400 mg. OF LIGNOCAINE ORALLY

SUBJECT NO.	HOURS AFTER INGESTION 1	2	3	4	5	6	8	10	12	24	APPARENT HALF-LIFE (HOURS)
1	0.86	0.62	0.44	0.31	0.22	0.16	0.078	0.046	0.021	0	2.08
2	0.68	0.48	0.34	0.24	0.17	0.11	0.063	0.026	0.019	0	2.06
3	0.58	0.47	0.34	0.30	0.20	0.13	0.070	0.036	0.022	0	2.22
4	0.95	1.27	0.81	0.55	0.42	0.20	0.144	0.066	0.028	0	1.90
5	0.65	1.06	0.63	0.46	0.40	0.36	0.170	-	0.05	0.011	2.39
6	-	0.99	-	0.65	-	0.53	0.340	-	0.16	0	3.85
7	-	0.46	-	0.18	-	0.08	0.030	-	-	0	1.54
8	-	0.64	-	0.29	-	0.12	0.022	0	0	0	1.26
MEAN	0.74	0.75	0.51	0.37	0.28	0.21	0.115	0.035	0.043	-	2.16
S.D.	0.15	0.31	0.20	0.16	0.12	0.16	0.105	0.020	0.054	-	0.77

c. GX

The plasma concentrations of GX in the individual subjects at the different sampling times are shown in Table XI. Of the 5 subjects who had hourly samples taken peak plasma GX concentrations occurred at 2 hours in one; at 3 hours in two and at 4 hours in 2 subjects respectively. The mean peak plasma concentration (0.23 µg/ml) was seen 3 hours after ingestion - range 0.12 - 0.42 µg/ml. The plasma concentrations fell slowly over the next 20 hours and 24 hours after ingestion 5 subjects still had detectable amounts of GX in their plasma (lower limit of detection of assay 0.03 µg/ml).

TABLE XI

PLASMA CONCENTRATIONS OF GX (µg/ml) IN HEALTHY SUBJECTS FOLLOWING 400 mg. OF LIGNOCAINE ORALLY

SUBJECT NO.	HOURS AFTER INGESTION									
	1	2	3	4	5	6	8	10	12	24
1	0.22	0.25	0.26	0.25	0.24	0.23	0.18	0.17	0.15	0.06
2	0.13	0.19	0.18	0.18	0.17	0.16	0.14	0.10	-	0.04
3	0.14	0.18	0.17	0.23	0.14	0.13	0.13	0.09	0.08	0.03
4	0.13	0.26	0.42	0.24	0.20	0.16	0.16	0.15	0.13	0
5	0.07	0.12	0.12	0.18	0.16	0.14	0.13	-	0.12	0.04
6	-	0.14	-	0.17	-	0.19	0.21	-	0.21	0
7	-	0.05	-	0.04	-	0.03	0.04	0.07	-	0
8	-	0.18	-	0.21	-	0.18	0.16	0.14	0.09	0.05
MEAN	0.14	0.17	0.23	0.19	.18	.15	.14	.12	.13	.03
S.D.	0.05	0.07	0.12	0.07	.04	.06	.05	.04	.05	.02

2. DISCUSSION

The peak plasma lignocaine concentrations occurring 1 hour after ingestion and the mean plasma lignocaine concentrations at the different sampling times are similar to previously published data in healthy subjects (Boyes et al., 1971; Adjepon-Yamoah, 1973).

The mean lignocaine half-life of 1.74 ± 0.28 hours is similar to the mean values of-

1.5 hours (Boyes et al., 1971; age of subjects 27 - 43 years)

1.71 ± 0.35 hours (Rowland et al., 1971; mean age of subjects 39 years)

1.8 hours (Thomson et al., 1973; age of subjects 24 - 57 years)

1.4 ± 0.02 hours (Adjepon-Yamoah, 1973)

previously reported in healthy subjects.

In this study the peak EGX concentrations occurred 1 or 2 hours after lignocaine ingestion. This is slightly later than the timing of peak plasma concentrations in a small group of healthy subjects reported by Adjepon-Yamoah (1973) where the peak plasma concentration was observed 45 mins. after drug ingestion. The mean apparent half-life of 2.16 ± 0.77 hours is, however, similar to that reported in healthy subjects by Adjepon-Yamoah (1973) of 2.3 ± 0.2 hours.

The mean peak plasma concentrations of GX and its occurrence 2 - 4 hours after the ingestion of lignocaine are also similar to previously published data in healthy subjects (Adjepon-Yamoah, 1973).

COMPARATIVE METABOLISM OF PARACETAMOL, ANTIPYRINE AND LIGNOCAINE IN HEALTHY SUBJECTS.

1. Results

As the plasma paracetamol and lignocaine and the plasma paracetamol and antipyrine half-lives were both measured in only 2 and 3 subjects respectively no meaningful correlations could be established between these two sets of half-lives.

The plasma lignocaine and antipyrine half-lives were both measured in 7 subjects. There was no correlation between the half-lives ($r = 0.12$; $p > 0.1$).

2. DISCUSSION

The failure in this study to demonstrate a correlation between the plasma half-lives of two drugs in healthy subjects is in keeping with the findings of other workers. Thus Vessel and Page (1968) could not demonstrate a correlation between the antipyrine half-life and that of phenylbutazone and dicoumarol, Davies and Thorgeirsson (1971) between the antipyrine and phenylbutazone half-lives and Kadar et al. (1973) between the glutethimide, amylobarbitone and sulphinpyrazone half-lives and the antipyrine half-life.

On the other hand some workers have demonstrated a correlation between the plasma half-lives of different drugs in healthy subjects. Thus Vessel and Page (1968) demonstrated a correlation between the plasma half-lives of phenylbutazone and dicoumarol, Hammar, Mårtens and Sjöqvist (1969) a correlation between the rate of metabolism of desmethylimipramine, nortriptyline and oxyphenylbutazone and Kadar et al. (1973) a correlation between the half-lives of glutethimide, amobarbital and sulphinpyrazone.

STUDIES IN PATIENTS WITH CHRONIC LIVER DISEASE

Twenty-three patients who had been admitted to hospital for investigation and/or treatment of chronic liver disease were studied after informed consent was obtained. The studies had been approved by the hospital ethical committee. The clinical details and diagnoses age given in Table XII. In 16 of the patients the diagnosis was established by liver biopsy or at autopsy. In the other 7 patients (Nos. 1, 8, 15, 16, 18, 19 and 23) the diagnosis was based on clinical and biochemical grounds. A prolonged prothrombin time ratio precluded a liver biopsy in patients 15, 16, 18, 19 and 23. All these patients however, had liver scans typical of cirrhosis.

The following indices of liver function were measured before the drugs were given: serum bilirubin and albumin concentrations, serum alanine aminotransferase (ALT) and alkaline phosphatase activities, and the prothrombin time ratio (P.T.R.). Respective normal values are 2 - 17 umol/l. (0.12 - 1.0 mg/100mls), 36 - 47 g/l., 10 - 40 U/l., 40 - 100 U/l. and 1.3 or less. If the prothrombin time ratio was greater than 1.3, vitamin K_1 (10 mg. intramuscularly) was given on two successive days and the P.T.R. re-measured. This vitamin-K_1- corrected P.T.R. was used in this study.

A complete drug history was taken and whenever possible all drugs were stopped before the studies began. Twelve patients had been taking drugs regularly: case 8 spironolactone and pethidine, case 14 bendrofluazide and spironolactone; case 18 spironolactone and protriptyline; case 16 bendrofluazide; cases 11, 15 and 22 frusemide and spironolactone; case 19 spironolactone, cases 11 and 23 prednisolone; case 9 cholestyramine and chlorpheniramine and case 13 pentobarbitone.

Patients 6, 8 and 11 did not drink alcohol whilst patients 3 - 5, 10 and 21 took less than 40 gm. per day. Patients 1 - 3, 7, 12, 14 - 20

14 - 20 and 22 were alcoholics and were drinking in excess of 120 gm. of alcohol per day. In all cases alcohol consumption stopped 2 - 4 weeks before the studies were carried out.

7 patients (nos. 7, 13, 15, 16, 19,22 and 23) were non-smokers whilst patients 5, 12 - 16, 18, 19 and 21 smoked 10 - 20 cigarettes per day until the time of and between the studies.

At the time of the studies, all patients were stable in their optimal clinical state and none was in cardiac failure. Only one patient (case 23) had a marginally raised blood urea concentration (44 mg/100 ml.). Five patients (cases 18, 19, 20, 22 and 23) had ascites and 6 (cases 2, 13, 14, 15, 16 and 22) oesophageal varices as judged by a barium swallow examination. Two patients (cases 6 and 8) had previously undergone porto-systemic shunt operations, the shunts being judged patent by the continuing absence of varices on a barium swallow examination. All patients were HBs Ag and HBs Ab negative.

The test drugs were administered consecutively 2 - 3 days apart over 7 - 10 days and were usually given in the sequence lignocaine, antipyrine and paracetamol. The studies were carried out as previously described as for healthy subjects (page 46,47). Patients were permitted to be ambulant during the studies and were not confined to bed.

For the purposes of comparison between different severities of liver disease the patients have been divided into three groups:-

Group 1 (patients 1 - 7 in Table XII) in whom the serum albumin and vitamin K_1 corrected P.T.R. were normal.

Group 2 (patients 8 - 13) in whom either the serum albumin or vitamin K_1 corrected P.T.R. were abnormal.

Group 3 (patients 14 - 23) in whom both the serum albumin and vitamin K_1 corrected P.T.R. were abnormal.

TABLE XI

CLINICAL AND LABORATORY DETAILS OF PATIENTS

Patient No.	Age (yrs)	Wt. (kg)	Sex	Diagnosis	Bilirubin (μmol/l)	ALT (units/l)	Alkaline phosphatase (units/l)	Albumin (gm/l)	Prothrombin Time ratio	Antipyrine Half-life (hours)	Paracetamol Half-life (hours)	Lignocaine Half-life (hours)
1	68	72	M	Alcoholic cirrhosis	30.8	43	315	45	1.2	-	-	2.3
2	49	56	M	Alcoholic cirrhosis	12.0	16	112	44	1.2	11.5	1.6	1.8
3	45	58	M	Alcoholic cirrhosis	17.1	14	119	43	1.0	-	-	4.3
4	41	57	F	Cryptogenic cirrhosis	12.0	22	182	42	1.0	4.9	1.7	1.8
5	67	64	M	Nodular transformation	17.1	17	98	39	1.0	9.8	1.9	4.6
6	27	51	F	Cryptogenic cirrhosis	18.0	101	350	36	1.2	15.5	4.0	6.1
7	51	76	M	Alcoholic cirrhosis	90.6	36	350	36	1.3	41.0	2.9	7.5
8	29	45	F	Sclerosing cholangitis	248.0	126	1085	34	1.2	14.0	-	5.0
9	43	54	F	Primary biliary cirrhosis	430.9	21	2625	32	1.1	12.3	-	2.6
10	54	53	F	Primary biliary cirrhosis	124.8	106	595	31	1.0	15.0	2.2	-
11	67	57	F	Chronic active hepatitis	95.8	200	119	31	1.3	23.7	3.1	4.1
12	29	66	M	Alcoholic cirrhosis	51.3	35	77	30	1.3	15.7	1.8	2.1
13	56	62	F	Primary biliary cirrhosis	42.8	48	560	27	1.3	11.0	2.2	3.2
14	60	60	M	Alcoholic cirrhosis	23.9	21	147	33	1.4	41.0	3.3	4.5
15	59	75	M	Alcoholic cirrhosis	37.6	21	84	33	1.6	37.0	3.6	9.0
16	52	76	F	Alcoholic cirrhosis	39.3	9	112	28	1.6	31.2	3.7	5.6
17	44	64	M	Alcoholic cirrhosis	99.2	38	154	26	2.0	-	-	7.1
18	48	52	F	Alcoholic cirrhosis	39.3	22	161	25	1.4	27.0	3.5	6.0
19	60	45	F	Alcoholic cirrhosis	114.6	24	168	25	1.9	49.0	6.5	12.4
20	60	67	M	Alcoholic cirrhosis	53.0	43	315	24	1.9	24.0	-	-
21	54	77	F	Chronic active hepatitis	47.9	103	329	22	1.4	56.0	5.1	13.2
22	55	66	M	Alcoholic cirrhosis	70.1	35	280	22	1.8	-	-	16.2
23	28	56	F	Chronic active hepatitis	201.8	21	1190	21	3.6	137.0	-	19.0
Mean	49.8	61.3			83.4	48.8	414.2	31.7	1.5	30.4	3.14	6.6
S.D.	12.6	9.6			96.7	47.0	565.9	7.3	0.6	29.6	1.4	4.83

CHAPTER 4

PARACETAMOL METABOLISM AND EXCRETION

1. Patients

Paracetamol metabolism and excretion was studied as previously described (page) in 16 patients (case nos. 2, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 18, 19 and 21 in Table XII). In patient no. 8, only urine samples were obtained, whilst in patient no. 19 plasma only was obtained.

2. Results:

a. Plasma

i. Plasma Paracetamol Concentrations

The plasma concentrations of paracetamol in the patients at the different sampling times are shown in Table XIII. The patients have been divided into three groups as previously described, based on the serum albumin and P.T.R. Patient no. 6, however, who had previously undergone a lieno-renal shunt was, despite a normal albumin and P.T.R. included in group 3 as the plasma paracetamol concentrations and plasma half-life were similar to patients in that group.

The mean plasma concentrations of paracetamol in groups 1, 2 and 3 were 10.8, 14.0 and 23.2 µg/ml respectively at 3 hours and 1.5, 2.3 and 8.6 µg/ml respectively at 9 hours after ingestion.

Figure 5 shows the mean (± S.E.M.) plasma paracetamol concentrations in the plasma of healthy subjects and the three groups of patients with liver disease. Patients in group 3 had a significantly higher level than those in groups 1, 2 or healthy subjects at all sampling times ($p \leq 0.01$). The initial mean paracetamol concentration in those with severe liver disease (group 3) was almost double that in the healthy subjects, whilst at 5, 7 and 9/

9 hours the ratios were 2.2, 3.0 and 3.7 respectively. There was no significant differences between the concentrations amongst groups 1 and 2 and healthy subjects at any of the sampling times except at 5 hours where group 1 had a significantly lower paracetamol concentration compared with healthy subjects only ($p < 0.02$).

ii. Plasam paracetamol half-life

The patients' plasma paracetamol half-life values are shown in Table XIII; the mean half-life in groups 1, 2 and 3 being 2.0, 2.3 and 4.2 hours respectively compared with the mean value of 2.4 $\pm$ 0.2 hours in healthy subjects. The plasma half-life values ranged from 1.6 to 6.5 hours.

All patients with a normal albumin and P.T.R. had a normal paracetamol half-life whilst in group 2 only one patient had a paracetamol half-life greater than normal i.e. more than the mean value $\pm$ 2 S.D. in healthy subjects. In group 3 all patients had an abnormal half-life.

The mean plasma paracetamol half-life in groups 1 and 2 were not significantly different from each other, or from the mean half-life in healthy subjects ($p > 0.05$). Those patients with severe liver disease (group 3) had, however, a significantly longer mean plasma paracetamol half-life than groups 1 and 2, and healthy subjects ($p < 0.001$).

In the patients as a whole there were significant correlations between the plasma paracetamol half-life and serum albumin ($r = -0.64$; $p < 0.02$), vitamin K_1 - corrected P.T.R. ($r = 0.79$; $p = < 0.01$), but not with A.L.T. ($r = 0.17$), alkaline phosphatase ($r = 0.21$) or serum bilirubin ($r = 0.02$) ($p > 0.1$).

TABLE XIII

PLASMA PARACETAMOL CONCENTRATIONS (µg/ml) AND HALF-LIFE VALUES (HOURS) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 1500 mg OF PARACETAMOL ORALLY

		HOURS AFTER INGESTION				
	PATIENT NO.	3	5	7	9	HALF-LIFE (HOURS)
GROUP 1	2	6.5	2.0	1.1	0.5	1.6
	4	8.8	3.2	1.2	0.8	1.7
	5	11.5	5.0	2.5	1.2	1.9
	7	16.2	6.7	4.8	3.6	2.9
	MEAN	10.8	4.2	2.4	1.5	2.02
	S.D.	4.2	2.1	1.7	1.4	0.59
GROUP 2	10	18.6	6.7	5.7	2.5	2.2
	11	14.5	7.3	4.7	3.7	3.1
	12	10.1	4.6	2.1	1.0	1.8
	13	12.8	7.1	3.7	1.9	2.2
	MEAN	14.0	6.4	4.1	2.3	2.32
	S.D.	3.6	1.2	1.5	1.1	0.55
GROUP 3	6	20.6	14.3	9.6	7.4	4.0
	14	20.0	12.7	8.5	5.6	3.3
	15	19.8	11.3	8.3	6.1	3.6
	16	21.9	13.9	10.7	7.0	3.7
	18	22.3	14.3	9.6	6.8	3.5
	19	29.9	24.5	20.4	15.6	6.5
	21	27.8	14.5	15.4	11.8	5.1
	MEAN	23.2	15.1	11.8	8.6	4.24
	S.D.	4.0	4.3	4.5	3.7	1.15
HEALTHY	MEAN	12.9	7.0	3.9	2.3	2.43
SUBJECTS	S.D.	2.2	1.4	0.9	0.5	0.19

iii. Paracetamol Metabolites in Plasma

The plasma concentrations of paracetamol glucuronide and paracetamol sulphate are shown in Tables XIV and XV respectively. The mean (± S.E.M.) concentrations are also shown in Figure 5 in comparison with the mean concentrations in healthy subjects.

At 3 hours the mean plasma glucuronide concentrations in groups 1, 2 and 3 were 24.2, 16.7 and 11.2 µg/ml respectively falling to 12.3, 9.4 and 10.4 at 9 hours. At 3 and 5 hours only the patients in group 1 had significantly higher concentrations than healthy subjects ($p < 0.005$) and those in group 3 ($p < 0.001$). There were no other significant differences between any of the other groups at any of the other sampling times, although those patients with the most severe disease (group 3) tended to have the lowest plasma concentrations.

With regard to paracetamol sulphate the mean plasma concentrations at 3 hours in group 1, 2 and 3 were 7.4, 5.6 and 4.3 µg/ml respectively falling to 3.6, 2.7 and 3.2 µg/ml at 9 hours. The only significant difference between the plasma concentrations in the 3 groups of patients and those in healthy subjects was at 9 hours when there was a higher concentration in group 3 than in healthy subjects ($p < 0.02$). Group 3 had the lowest mean plasma concentration at 3 hours and the highest at 9 hours; group 1 having the highest mean concentration at 3 hours (Fig. 5).

The ratios of plasma paracetamol to paracetamol glucuronide in the 3 groups of patients and the healthy subjects are shown in Table XVI. Group 1 had, at all sampling times, a lower ratio than healthy subjects reflecting the increased plasma paracetamol half-life in that group and increased glucuronide formation. In group 2 the ratios were similar to those of healthy subjects. In group 3 the ratios were higher than in healthy subjects, reflecting the prolonged plasma half-life and slower glucuronide formation.

TABLE XIV

PLASMA PARACETAMOL GLUCURONIDE CONCENTRATIONS (µg/ml) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 1500 mg. OF PARACETAMOL ORALLY

		HOURS AFTER INGESTION			
	PATIENT NO.	3	5	7	9
GROUP 1	2	30.4	22.6	14.5	11.8
	4	23.7	15.7	6.9	3.4
	5	26.4	24.6	20.2	13.9
	7	16.3	9.9	7.4	6.8
	MEAN	24.2	18.2	12.3	9.0
	S.D.	5.9	6.7	6.3	4.8
GROUP 2	10	22.3	13.1	18.8	11.9
	11	11.7	7.2	5.5	5.3
	12	18.5	10.9	5.4	3.4
	13	14.3	9.9	8.0	3.2
	MEAN	16.7	10.3	9.4	6.0
	S.D.	4.7	2.4	6.4	4.1
GROUP 3	6	5.4	5.8	4.6	3.3
	14	9.5	9.9	8.5	6.5
	15	10.9	12.0	10.9	10.8
	16	5.7	5.7	4.7	3.8
	18	25.6	18.5	16.3	12.9
	19	6.6	7.9	7.7	6.8
	21	15.0	14.4	20.4	17.6
	MEAN	11.2	10.6	10.4	8.8
	S.D.	7.2	4.7	5.9	5.2
HEALTHY	MEAN	14.3	11.6	7.7	4.9
SUBJECTS	S.D.	3.3	2.7	2.1	1.3

TABLE XV

PLASMA PARACETAMOL SULPHATE CONCENTRATIONS (µg/ml) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 1500mg. OF PARACETAMOL ORALLY

		HOURS AFTER INGESTION			
	PATIENT NO.	3	5	7	9
GROUP 1	2	6.8	4.4	2.2	1.5
	4	6.5	3.4	1.5	0.8
	5	11.5	9.2	7.1	4.6
	7	4.7	3.4	2.6	2.0
	MEAN	7.4	5.1	3.4	2.2
	S.D.	2.9	2.8	2.5	1.7
GROUP 2	10	9.2	5.1	6.2	3.4
	11	5.3	3.1	2.3	2.1
	12	4.5	2.7	1.3	0.7
	13	3.2	2.2	0.9	0.3
	MEAN	5.6	3.3	2.7	1.6
	S.D.	2.6	1.3	2.4	1.4
GROUP 3	6	2.2	2.9	1.5	1.3
	14	6.2	5.3	4.5	2.8
	15	4.8	2.5	3.5	2.8
	16	3.0	2.9	2.7	1.8
	18	8.1	4.8	4.1	2.8
	19	2.9	3.8	3.6	3.2
	21	2.6	2.1	2.2	2.5
	MEAN	4.3	3.5	3.2	2.5
	S.D.	2.2	1.2	1.1	0.7
HEALTHY	MEAN	4.7	3.6	2.3	1.5
SUBJECTS	S.D..	1.8	1.3	0.9	0.7

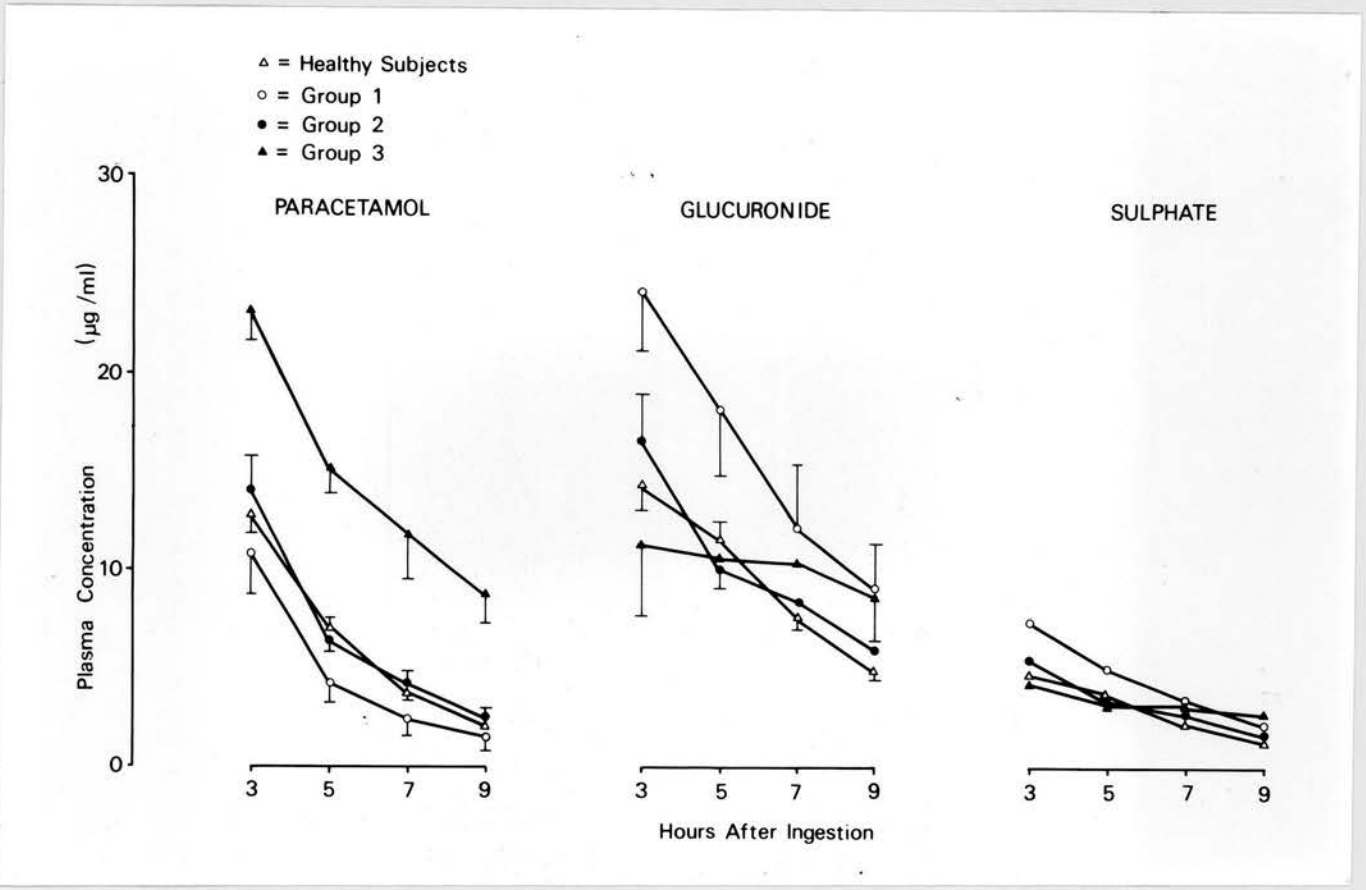

Fig. 5

Plasma concentrations of paracetamol and its glucuronide and sulphate conjugates in healthy subjects and 3 groups of patients with different severity of chronic liver disease after a single oral dose of 1.5g. Concentrations of conjugates are expressed as paracetamol equivalents. (Mean ± S.E.M.)

TABLE XVI

RATIO OF PLASMA PARACETAMOL/PARACETAMOL GLUCURONIDE CONCENTRATIONS IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 1500 mg. OF PARACETAMOL ORALLY

HOURS AFTER INGESTION	HEALTHY SUBJECTS	PATIENTS GROUP 1	GROUP 2	GROUP 3
3	0.90	0.44	0.83	2.06
5	0.60	0.23	0.49	1.42
7	0.51	0.19	0.24	1.12
9	0.47	0.16	0.38	0.98

The ratios of plasma paracetamol to paracetamol sulphate in the 3 groups of patients and in healthy subjects is shown in Table XVII. A similar pattern to that of plasma glucuronide is seen with group 1 having much lower ratios than healthy subjects at all sampling times and group 3 higher ratios.

The ratios of plasma paracetamol glucuronide to paracetamol sulphate concentrations in the 3 groups of patients and in healthy subjects are shown in Table XVIII. Although in all the groups and in healthy subjects there was an increase in the ratios with time, there was little difference in these ratios between the 3 groups and the healthy subjects.

TABLE XVII

RATIO OF PLASMA PARACETAMOL/PARACETAMOL SULPHATE CONCENTRATIONS IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 1500mg OF PARACETAMOL ORALLY

HOURS AFTER INGESTION	HEALTHY SUBJECTS	PATIENTS GROUP 1	PATIENTS GROUP 2	PATIENTS GROUP 3
3	2.73	1.46	3.35	5.46
5	1.94	0.83	1.96	4.31
7	1.71	0.72	1.52	3.74
9	1.61	0.68	1.54	3.51

TABLE XVIII

RATIO OF PLASMA PARACETAMOL GLUCURONIDE/PARACETAMOL SULPHATE CONCENTRATIONS IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 1500 mg OF PARACETAMOL ORALLY

HOURS AFTER INGESTION	HEALTHY SUBJECTS	PATIENTS GROUP 1	GROUP 2	GROUP 3
3	3.03	3.28	3.01	2.64
5	3.20	3.56	3.14	3.03
7	3.60	3.66	3.53	3.31
9	3.83	4.04	3.67	3.60

b. Urinary Excretion of Paracetamol and Metabolites

The urine volumes and the urinary excretion of paracetamol and its metabolites in the three groups of patients with liver disease are shown in Table XIX. The excretion of these compounds expressed as a percentage of the ingested dose and compared with that in healthy subjects is shown in Table XX.

There were no significant differences between the total recovery of paracetamol and its metabolites between the three groups of patients. However, compared with healthy subjects the total recovery in group 2 (79%) was significantly reduced ($p < 0.001$). There were no significant differences in the urinary volumes between the three groups, but compared with healthy subjects the urine volume in group 2 was increased ($p = 0.02$).

Although the excretion of unchanged paracetamol was less in group 1 and higher in group 3 than in healthy subjects these differences just failed to reach statistical significance ($p > 0.05$). There was also no significant difference between the excretion of unchanged paracetamol between groups 1 and 3 ($p > 0.05$). With regard to the excretion of paracetamol metabolites the only significant difference observed in the three groups and the healthy subjects was in the sulphate excretion where group 3 excreted significantly more sulphate than group 1 ($p < 0.05$). Although group 1 did excrete much less sulphate than healthy subjects this was not a significant difference ($p > 0.05$).

TABLE XIX

24-HOUR URINARY RECOVERY OF UNCHANGED PARACETAMOL AND ITS METABOLITES (mg) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 1500 mg. OF PARACETAMOL ORALLY.

	PATIENT NO.	UNCHANGED PARACETAMOL	PARACETAMOL GLUCURONIDE	PARACETAMOL SULPHATE	PARACETAMOL MERCAPTURATE CONJUGATE	PARACETAMOL CYSTEINE CONJUGATE	TOTAL EXCRETION	% RECOVERY	URINE VOLUME cc
GROUP 1	2	26.4	713	276	31.1	13.9	1060	70.7	1640
	4	12.2	817	240	57.1	60.4	1187	79.1	778
	5	47.8	873	424	47.6	86.7	1479	98.6	767
	7	24.1	792	379	64.6	61.6	1321	88.1	1351
	MEAN	27.6	798.8	178.7	50.1	55.7	1261	84.1	1134
	S.D.	14.8	66.4	171.3	14.5	30.4	179.8	12.0	433
GROUP 2	8	51.6	740	486	26.6	33.8	1338	89.2	2550
	10	23.9	579	308	102.6	69.0	1083	72.2	1509
	11	34.9	503	425	57.7	64.3	1085	72.3	2046
	12	23.7	789	342	34.8	36.0	1226	81.7	2385
	13	48.7	741	295	37.3	62.0	1184	78.9	1155
	MEAN	36.6	670.4	371.2	68.6	53.0	1183.2	78.9	1929
	S.D.	13.3	122.8	81.7	28.6	16.8	106.6	7.1	588
GROUP 3	6	68.5	633	425	70.8	93.3	1291	86.0	997
	14	27.0	473	456	46.7	43.7	1046	69.8	1323
	15	27.6	761	495	19.3	18.2	1321	88.1	682
	16	64.1	464	438	55.2	53.1	1074	71.6	1371
	18	105.0	941	473	53.1	33.3	1605	107.0	2990
	21	77.0	778	287	31.0	67.2	1240	82.7	1736
	MEAN	61.5	675.0	429.0	46.0	51.5	1262.8	84.2	1517
	S.D.	30.1	187.5	73.9	18.4	26.5	202.2	13.5	806
HEALTHY SUBJECTS	MEAN	49.9	751	459	66.6	52.6	1379	91.9	1163
	S.D.	17.3	149	110	22.1	13.1	59.7	4.0	441

TABLE XX

24-HOUR EXCRETION OF PARACETAMOL AND ITS GLUCURONIDE, SULPHATE, MERCAPTURATE AND CYSTEINE METABOLITES (AS % OF DOSE) IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 1500 mg. OF PARACETAMOL ORALLY.

VALUES ARE MEANS ± S.D.

	UNCHANGED PARACETAMOL	PARACETAMOL GUCURONIDE	PARACETAMOL SULPHATE	PARACETAMOL MERCAPTURATE CONJUGATE	PARACETAMOL CYSTEINE CONJUGATE	TOTAL EXCRETION
HEALTHY SUBJECTS (n=8)	3.3 ± 1.2	50.1 ± 9.9	30.6 ± 7.3	4.4 ± 1.5	3.5 ± 0.9	91.9 ± 4.0
GROUP 1 (n=4)	1.8 ± 1.0	53.3 ± 4.4	22.0 ± 11.4	3.3 ± 1.0	3.7 ± 2.0	84.1 ± 12.0
GROUP 2 (n=5)	2.4 ± 0.9	44.7 ± 8.2	24.7 ± 5.4	4.6 ± 1.9	3.5 ± 1.1	78.9 ± 7.1
GROUP 3 (n=6)	4.1 ± 2.0	45.0 ± 12.5	28.6 ± 4.9	3.1 ± 1.2	3.4 ± 1.8	84.2 ± 13.5

c. Lieno-Renal shunt Patients (nos 6 and 8)

The plasma paracetamol half-life was prolonged (4.0 hours) in patient no. 6 despite a normal albumin and P.T.R. The plasma concentrations of paracetamol and its glucuronide and sulphate conjugates are shown in Fig. 6. The initial plasma paracetamol concentration (20.6 µg/ml) was 1.6 times higher than the mean concentration observed in healthy subjects and higher than any of the concentrations in groups 1 and 2. In conjunction with this there were very low plasma concentrations of glucuronide and sulphate. The initial plasma glucuronide (5.4 µg/ml) and plasma sulphate (2.2 µg/ml) concentrations were the lowest observed in all the patients, being approximately one third and one half respectively of the concentrations in healthy subjects.

The urinary excretion of unchanged paracetamol in both patients was higher than in the patients with mild liver disease (groups 1 and 2); there being no differences in the excretion of metabolites.

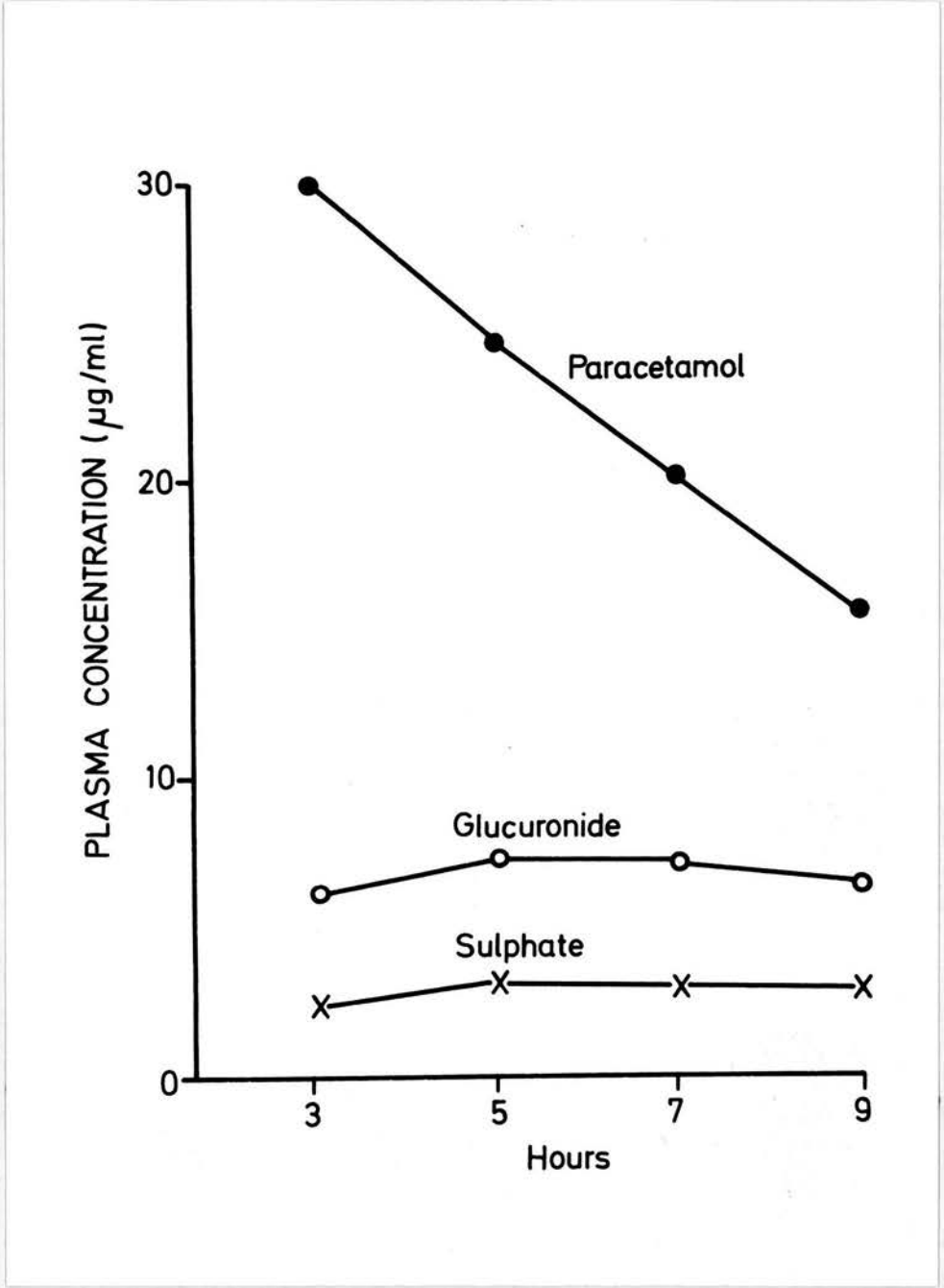

Fig. 6

Plasma concentrations of paracetamol and its glucuronide and sulphate conjugates after a single oral dose of 1.5g in a patient with a porto-systemic shunt (case no. 6).

3. DISCUSSION

Although it is a widely used analgesic there has apparently been only one previous study of the metabolism of paracetamol in patients with liver disease (Shamszad et al., 1975). In this study in patients with different degrees of alcoholic liver disease, the plasma paracetamol half-life was prolonged in patients with cirrhosis and acute alcoholic hepatitis but not in those alcoholics with normal liver function tests.

In the present study the plasma paracetamol half-life in patients with a normal serum albumin and/or P.T.R. was not significantly different from that in healthy subjects; only 1 of 8 patients having a plasma half-life outwith the range observed in healthy subjects. Indeed the mean half-life in those patients with a normal serum albumin and P.T.R. (group 1) was somewhat less than that in the healthy subjects even suggesting an increased rate of metabolism. This may be due to microsomal enzyme induction caused by alcohol consumption as all 4 patients in that group had been taking significant quantities of alcohol regularly until 2 - 3 weeks prior to the study. None, however, had been taking any medications although 1 of the 4 smoked cigarettes.

In contrast, in those patients with severe liver disease where both the serum albumin and P.T.R. were abnormal (group 3) all patients had a prolonged half-life. As the mean age of the patients in this group (52 years) was almost identical with that in group 1 (51 years) this factor cannot explain the prolonged plasma half-life of group 3.

Thus in the patients overall there were significant correlations between the plasma paracetamol half-life and the serum albumin and P.T.R. but not with the serum bilirubin, A.L.T. or alkaline phosphatase. The plasma half-life, therefore, correlated with markers of the capacity of the liver for protein synthesis.

The plasma concentrations of the glucuronide metabolite in the 3 groups of patients are inversely related to the plasma paracetamol half-life. Thus in group 1 there was a faster rate of glucuronide production with significantly higher plasma concentrations at the time of the initial venous sample than in the healthy subjects. In group 3 the mean plasma concentration was less than in the healthy subjects, although this was not a statistically significant change. Although there were no significant differences in the initial plasma paracetamol sulphate concentrations between any of the 3 groups of patients and the healthy subjects, group 1 had a higher and group 3 a lower mean concentration than the healthy subjects. These differences are reflected in the paracetamol to paracetamol glucuronide and paracetamol sulphate ratios. Thus group 1 had, at all sampling times, lower ratios and group 3 much higher ratios than the healthy subjects, reflecting the different rates of metabolism of unchanged paracetamol to the glucuronide and sulphate metabolites.

With regard to the unchanged plasma paracetamol concentrations there was no significant differences, at the time of the initial sample, between the plasma concentrations in groups 1 and 2 and the healthy subjects. However, the mean value in group 1 was slightly less than that of the healthy subjects. In those with severe disease, however, the mean plasma concentration was more than double that of group 1.

Although the hepatic extraction ratio of paracetamol is low (0.10 - 0.20) the higher initial plasma concentrations of unchanged drug in the patients with severe liver disease suggests that this may be due in part to a reduced "first-pass" hepatic metabolism during absorption, secondary to a reduced effective liver blood flow.

In this context it is of interest that in the patients studied the presence of portal hypertension per se (as judged by a barium swallow examination) was not necessarily associated with an increased initial plasma paracetamol concentration or plasma half-life. However, in the patient with the lieno-renal shunt there was evidence of markedly reduced "first-pass" metabolism. Thus although the patient had a normal serum albumin and P.T.R. the initial plasma paracetamol concentration was very high, with slow metabolism, a prolonged half-life and very low plasma concentrations of the metabolites. From the therapeutic point of view the results show that care must be taken in prescribing drugs - especially those with high hepatic extraction ratios - to patients with severe liver disease and/or where there is evidence of porto-systemic shunting as repeated doses could lead to cumulation and toxicity.

There were no significant differences between the total urinary recovery of unchanged paracetamol and its metabolites between the 3 groups of patients; only group 2 excreting less than the healthy subjects. Although the total excretion of unchanged paracetamol was less in group 1 and more in group 3 than in healthy subjects - reflecting the plasma concentrations - these just failed to reach statistical significance. With regard to the excretion of the metabolites, the only sifnificant difference was in the sulphate excretion where group 3 excreted more sulphate than group 1.

Of particular significance is the excretion even in group 3, of normal amounts of the cysteine and mercapturic acid conjugates. These two metabolites reflect conversion of the drug to the reactive hepatotoxic intermediate which undergoes conjugation with reduced glutathione (Mitchell et al., 1973 a and b; Jollow et al., 1973; Potter et al., 1973).

With increasing hepatotoxic doses of paracetamol the cysteine and mercapturic acid conjugates are excreted in proportionally larger amounts (Howie, Adriaenssens and Prescott, 1977; Davis et al., 1976) and the present findings provide no evidence to suggest that a therapeutic dose of paracetamol is more likely to cause liver damage in patients with chronic liver disease than in healthy subjects. However, this possibility cannot be ruled out completely as the threshold dose of paracetamol required to produce liver damage depends on the balance of many factors including the rate of paracetamol absorption, the rate of production of the toxic metabolite, hepatic glutathione stores and the maximum rate of glutathione synthesis, all of which could be abnormal in liver disease. Furthermore, the study was carried out with single doses only. If the intracellular concentrations of glutathione and its rate of synthesis were to be depressed in patients with severe liver disease repeated therapeutic doses of paracetamol could conceivably cause further liver damage. In this context it should be noted that toxic hepatitis has been reported in patients said to have taken high therapeutic doses of the drug. (Barker, de Colle and Anuras, 1977 ; Johnson and Tolman, 1977).

4. SUMMARY

The plasma concentrations and 24 hour urinary excretion of paracetamol and its glucuronide, sulphate, cysteine and mercapturic acid conjugates were measured in 16 patients with chronic liver disease and compared with those in healthy subjects.

At the time of the initial venous sample (3 hours) those patients wtih an abnormal serum albumin and P.T.R. had significantly higher plasma paracetamol concentrations than patients in whom the serum albumin and/or P.T.R. was normal and the healthy subjects. Thus in the patients with severe liver disease there was evidence of reduced first pass metabolism; this also being seen in a patient who had undergone a lieno-renal shunt. Patients with severe liver disease tended to have the lowest plasma glucuronide concentrations.

The mean plasma paracetamol half-life was similar in normal subjects (2.4 $\pm$ 0.2 hours) and in patients where the serum albumin and P.T.R. were normal (2.0 $\pm$ 0.6 hours) and where one of these factors was abnormal (2.3 $\pm$ 0.6 hours). It was, however, significantly prolonged in patients who had an abnormal serum albumin and P.T.R. (4.2 $\pm$ 1.2 hours). Prolongation of the paracetamol half-life was related to a reduced serum albumin and increased P.T.R. The mean ratios of plasma concentrations of unchanged paracetamol to paracetamol glucuronide and sulphate were less in patients with mild and greater in patients with severe liver disease than the healthy subjects.

There were no significant differences in the 24 hour urinary excretion of unchanged paracetamol and its glucuronide, cysteine and mercapturate acid conjugates in the 3 groups of patients and the healthy subjects, although those with severe liver disease excreted more sulphate than those with a normal serum albumin and P.T.R. The glutathione conjugation of paracetamol did not seem to be impaired even in patients with severe liver disease as evidenced by the production of normal amounts/

amounts of the cysteine and mercapturic acid conjugates. There is thus no evidence that such patients are at increased risk of hepatotoxicity when given a single therapeutic dose of paracetamol.

CHAPTER 5
ANTIPYRINE METABOLISM

1. Patients

The elimination of antipyrine from the plasma was studied in 19 patients with chronic liver disease (case numbers 2, 4 - 16, 18 - 21 and 23 in Table XII). The study was performed as previously described for healthy subjects (pages 46,47) except that blood samples were also obtained at 36 and 48 hours after drug ingestion.

2. Results

a. Plasma antipyrine concentrations

The plasma antipyrine concentrations in the individual patients at the different sampling times are shown in Table XXI. The mean 4 hour plasma antipyrine concentrations in group 1, 2 and 3 were 28.2, 29.0 and 29.2 µg/ml respectively, there being no significant differences between any of the groups ($p > 0.05$). All 3 groups of patients, had, however significantly higher concentrations at this time than those in healthy subjects (mean 22.3 µg/ml) (group 1 vs. normal subjects $p < 0.02$; groups 2 and 3 vs. normal subjects $p < 0.005$). The mean ($\pm$ SEM) plasma antipyrine concentrations in the 3 groups of patients and in healthy subjects are shown in Fig. 7.

There were no significant differences between the plasma concentrations in the 3 groups of patients at 8 and 12 hours. At 24, 36 and 48 hours group 3 had significantly higher plasma concentrations than groups 1 and 2 ($p \leq 0.05$); there being no significant differences between these two groups.

In comparison with the plasma concentrations seen in healthy subjects all groups of patients had significantly higher concentrations at 8 hours, but at 12 and 24 hours only groups 2 and 3 had significantly higher concentrations.

TABLE XXI

PLASMA ANTIPYRINE CONCENTRATIONS (μg/ml), HALF-LIFE VALUES (HOURS) AND CLEARANCE (ml/min) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING ANTIPYRINE (18mg/kg) ORALLY.

		HOURS AFTER INGESTION						PLASMA HALF-LIFE (HOURS)	PLASMA CLEARANCE (ml/min)
	PATIENT NO.	4	8	12	24	36	48		
GROUP 1	2	21.0	17.6	13.2	6.4	3.1	1.5	11.5	36.8
	4	22.9	13.9	8.1	1.9	0.4	0.1	5.6	57.4
	5	31.5	23.2	16.1	6.7	2.7	1.5	9.8	34.7
	6	30.1	24.7	21.0	12.0	6.9	3.9	15.8	18.5
	7	35.4	33.2	28.6	26.5	20.3	15.6	40.0	10.4
	MEAN	28.2	22.5	17.4	10.7	6.7	4.5	16.5	31.6
	S.D.	6.0	7.4	7.8	9.5	8.0	6.3	13.6	18.2
GROUP 2	8	37.2	30.5	24.4	13.8	7.6	4.2	14.0	14.9
	9	25.0	20.0	15.2	7.1	3.3	1.5	11.1	30.8
	10	26.2	23.1	20.6	11.5	6.3	3.8	15.3	21.7
	11	29.6	26.1	21.8	15.9	11.3	8.2	23.8	15.4
	12	23.3	20.3	18.1	9.9	5.9	3.5	15.7	30.3
	13	32.6	25.5	20.0	9.6	4.6	2.1	11.3	28.0
	MEAN	29.0	24.3	20.0	11.3	6.5	3.9	15.2	23.2
	S.D.	5.2	4.0	3.1	3.2	2.8	2.4	4.6	7.2
GROUP 3	14	26.0	24.4	23.0	18.5	15.8	13.4	44.3	10.3
	15	28.3	25.4	25.9	19.8	17.7	15.2	47.4	11.2
	16	35.8	32.2	32.0	23.7	18.3	13.7	31.7	12.6
	18	33.4	28.6	25.5	17.8	14.4	8.2	23.7	12.3
	19	35.5	33.2	31.5	26.1	21.9	17.9	45.9	5.4
	20	22.6	19.8	17.7	12.3	8.6	6.0	23.0	23.9
	21	32.1	32.1	30.9	29.0	23.6	20.0	56.0	8.2
	23	19.5	18.1	17.9	17.3	16.1	15.1	137.0	4.4
	MEAN	29.2	26.7	25.6	20.6	17.1	13.7	51.1	11.0
	S.D.	6.1	5.8	5.8	5.4	4.6	4.6	36.7	6.0
HEALTHY SUBJECTS	MEAN	22.3	17.3	13.7	6.5	-	-	11.6	43.8
	S.D.	1.6	1.2	1.4	1.6	-	-	2.8	5.7

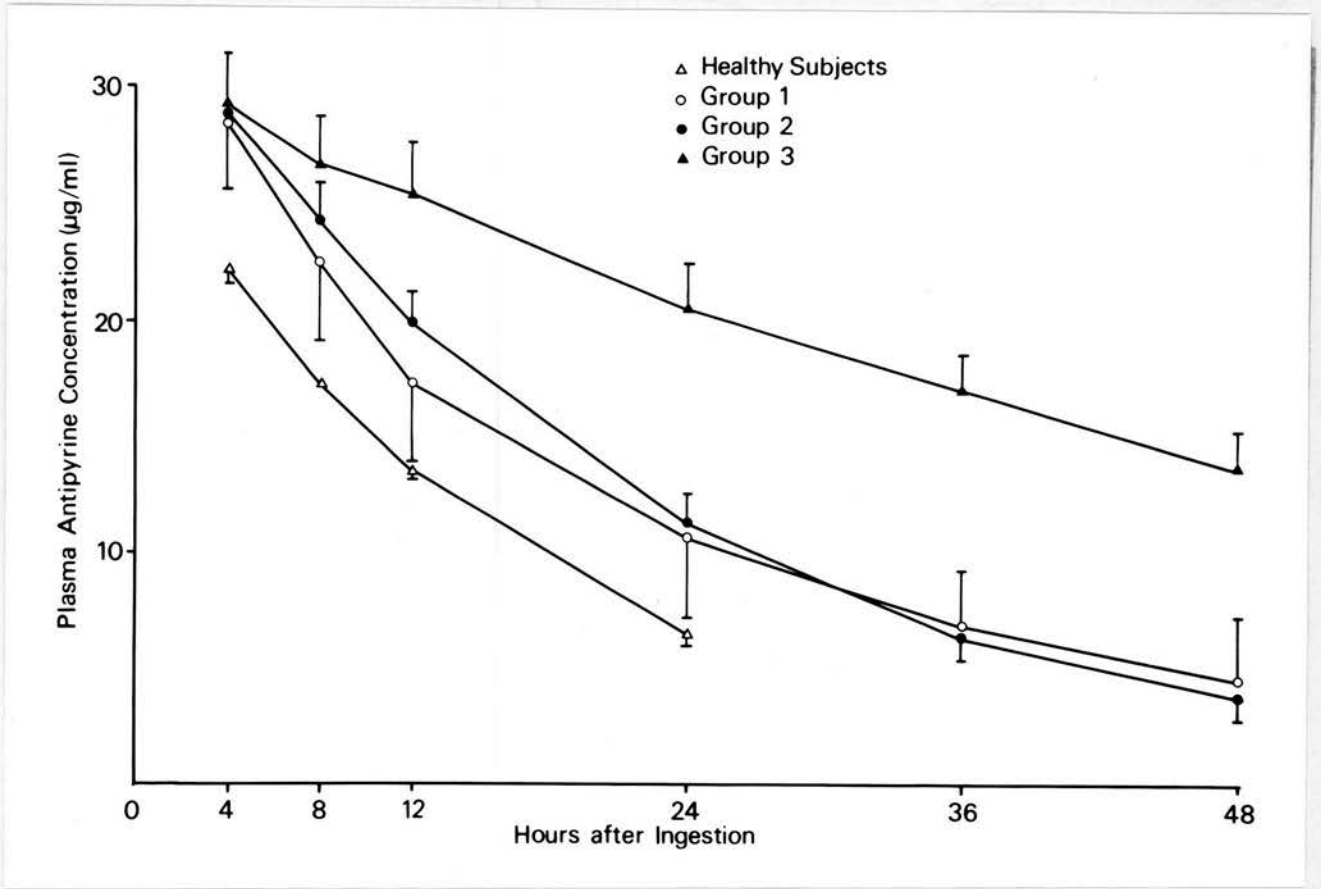

Fig. 7

Plasma antipyrine concentrations in healthy subjects and 3 groups of patients with different severity of chronic liver disease after a single oral dose (18 mg/kg body wt.) ; (Mean ± S.E.M.)

b. Plasma antipyrine half-lives

The mean plasma antipyrine half-life values in groups 1, 2 and 3 (Table XXI) were 16.5, 15.2 and 51.1 hours respectively, compared with a mean value of 11.6 $\pm$ 2.8 hours in healthy subjects. In groups 1 and 2 only one patient in each group had a plasma half-life outwith the range found in healthy subjects whilst all patients in group 3 had significantly prolonged half-lives. The shortest half-life was 5.6 hours, the longest being 137 hours.

There was no significant difference in the plasma antipyrine half-life between groups 1 and 2 ($p = 0.9$) or between these groups and the half-life in healthy subjects ($p > 0.1$). The half-life of group 3, however was, significantly prolonged compared with groups 1 and 2 ($p < 0.05$) and healthy subjects ($p < 0.005$).

Considering all the patients together there were significant correlations between the plasma antipyrine half-life and serum albumin ($r = -0.55$; $p < 0.02$) and the vitamin K_1 corrected P.T.R. ($r = 0.91$; $p < 0.001$) but not with serum bilirubin ($r = 0.13$), A.L.T. ($r = 0.14$) or alkaline phosphatase ($r = 0.10$).

c. Volume of distribution

The volume of distribution in groups 1, 2 and 3 was 31.1 ± 5.1 litres, 29.2 ± 7.5 litres, and 38.2 ± 10.8 litres respectively; there being no significant differences between any of the groups ($p \geq 0.2$). Compared with the values in healthy subjects (43.2 ± 7.7 litres) groups 1 and 2 had significantly smaller volumes of distribution ($p < 0.01$ and < 0.005) respectively); group 3 not being significantly different.

In conjunction with this the plasma concentrations at time zero in groups 1, 2 and 3 were 35.5 ± 4.6 µg/ml, 35.7 ± 6.3 µg/ml and 31.4 ± 7.2 µg/ml respectively, there being no significant difference between any of the groups ($p > 0.3$). Compared with the values observed in healthy subjects (28.9 ± 3.8 µg/ml) groups 1 and 2 had significantly higher plasma concentrations at time zero ($p < 0.02$); group 3 not being significantly different.

d. Plasma clearance of antipyrine

The plasma clearance of antipyrine in groups 1, 2 and 3 was 31.6 ± 18.2, 23.3 ± 7.2 and 11.0 ± 6.0 mls/min respectively (Table XXI); group 3 being significantly slower than groups 1 and 2 ($p < 0.02$ and < 0.005 respectively). There was no significant difference between groups 1 and 2 ($p > 0.3$). Compared with the values observed in healthy subjects (43.8 ± 5.7 mls/min) groups 2 and 3 only had significantly slower clearances ($p \leq 0.001$).

Considering all the patients together there was a significant correlation between the plasma clearance of antipyrine and the serum albumin ($r = 0.62$; $p < 0.01$) but not with the vitamin K_1-corrected P.T.R. ($r = 0.23$), serum bilirubin (0.18), A.L.T. ($r = 0.17$) or alkaline phosphatase ($r = 0.1$).

3. DISCUSSION

In this study the plasma antipyrine half-life in patients with mild and moderate liver disease (groups 1 and 2) was not significantly different from each other or from the half-life in healthy subjects. Of the 11 patients in these two groups only two had plasma half-lives outwith the normal range. In those with severe liver disease, however the plasma half-life was significantly prolonged compared with healthy subjects and also groups 1 and 2. In this group all patients had half-lives outwith the normal range.

The volume of distribution of antipyrine was not significantly different between the 3 groups of patients, but in those with mild and moderate-disease was less than in healthy subjects. These findings appear to be different from those of Branch, James and Read (1976a) who found the volume of distribution of antipyrine to be similar in control subjects and two groups of patients (serum albumin greater than and less than 30 gm/l) with chronic liver disease. In addition Andreasen et al (1974) noted the volume of distribution to be similar in normal subjects and patients with chronic liver disease of varying severity. However, in both these studies the patients were not grouped as in this study and this may explain the discrepancy between the results.

In association with the plasma half-life the plasma clearance of antipyrine in patients with severe liver disease was significantly less than in those with mild and moderate liver disease in whom there was no significant difference in the clearance.

The findings of this study in relation to the plasma half-life and clearance of antipyrine are in keeping with previous studies on antipyrine elimination in patients with liver disease. Thus Brodie, Burns and Weiner (1959) and Andreasen and Vesell (1974) failed to demonstrate a prolongation of the plasma antipyrine half-life in patients with cirrhosis.

In addition, Farrell et al. (1978) noted that the plasma half-life was usually normal in patients with compensated cirrhosis; this also being found in this study. There are two possible explanations for these findings. Firstly, that despite cirrhosis being present, there are still sufficient functioning hepatocytes to metabolise the drug at a normal rate. Secondly, the patients may have been exposed to inducing agents such as drugs, cigarettes and/or alcohol, which have acted to induce the enzymes in a reduced number of functioning hepatocytes. In this study 27% of those in groups 1 and 2 smoked cigarettes and 64% had been taking alcohol regularly until a few weeks before the study. Only 3 of the 11 patients in these two groups had, however, been taking drugs known to induce microsomal enzymes.

In this study there was a prolonged plasma half-life and a reduced plasma clearance of antipyrine in patients with severe liver disease, this also having been reported in patients with various forms of liver disease (Branch, James and Read, 1973 ; Andreasen et al., 1974; Branch, James and Read, 1976a; Farrell et al., 1978). Thus in patients with a range of hepatic disorders Branch, James and Read (1973) noted the plasma half-life to be 26.5 $\pm$ 4.6 hours compared with 12.0 $\pm$ 1.7 hours in healthy subjects. However, in those with cirrhosis the plasma half-life was more prolonged at 33.8 $\pm$ 6.8 hours.

In the present study there were significant correlations between the plasma antipyrine half-life and the serum albumin and P.T.R. but not with any of the other liver function tests. This is in agreement with the findings of other workers (Branch, James and Read, 1973 ; Andreasen et al., 1974; Branch, James and Read, 1976a Farrell et al., 1978). In addition, however, Branch,James and Read (1976a) and Farrell et al., (1978) noted a correlation between the plasma half-life and plasma clearance of the drug and the serum bilirubin; this not being found in this study.

The concept of a correlation between the synthetic capacity of the liver (as manifest by the serum albumin and P.T.R.) and the plasma antipyrine half-life is further strengthened by the work of Sotaniemi et al., (1977) and Pirrttiaho et al., (1978) who demonstrated a good correlation between the "in vivo" antipyrine half-life and the cytochrome P450 activity; since the amount of the enzyme depends on the synthetic capacity of the liver also.

It is of interest that the two patients with lieno-renal shunts (nos 6 and 8) had plasma half-lives in the normal range. This would support the theoretical concept that, because of the drug's low hepatic extraction ratio, its rate of elimination is not dependent on effective liver blood flow but on the activity of the drug metabolising enzymes.

The plasma antipyrine concentrations at the time of the initial sample (4 hours) are of interest. There were no significant differences between the plasma concentrations in the 3 groups of patients. This is what would be predicted for a drug with a low hepatic extraction ratio, where its rate of removal by the liver is not dependent on effective liver blood flow which will be reduced the more severe the liver disease. However, the 4 hour plasma concentration in all 3 groups of patients was significantly higher than in the healthy subjects. In groups 1 and 2 this may be due to a more rapid absorption of the drug as the plasma concentrations at time zero were higher in these groups than in the healthy subjects. In those with severe liver disease however, the plasma concentrations at time zero were not higher than the healthy subjects and the higher plasma concentrations at 4 hours may be due to the significantly slower metabolism in this group.

4. SUMMARY

The plasma half-life, volume of distribution and plasma clearance of antipyrine was determined in 19 patients with chronic liver disease following antipyrine (18 mg/kg) orally. The plasma half-life was similar in those patients with a normal plasma albumin and P.T.R. (group 1) (16.5 ± 13.6 hours) and those in whom one of these indices was abnormal (group 2) (15.2 ± 4.6 hours) and healthy subjects (11.6 ± 2.8 hours), but was significantly prolonged in those in whom both indices were abnormal (group 3) (51.1 ± 36.7 hours).

In conjunction with this the plasma antipyrine clearance was significantly greater in groups 1 (31.6 ± 18.2 mls/min); 2 (23.2 ± 7.2 mls/min) and healthy subjects (28.9 ± 3.8 mls/min) than group 3 (11.0 ± 6.0 mls/min). There were no significant differences in the volume of distribution between the 3 groups, although groups 1 and 2 had significantly smaller volumes of distribution than the healthy subjects.

Significant correlations were demonstrated only between theplasma antipyrine half-life and the serum albumin and vitamin K_1-corrected P.T.R. and between the plasma clearance of antipyrine and the serum albumin.

CHAPTER 6

LIGNOCAINE METABOLISM AND EXCRETION

1. Patients

Lignocaine metabolism and excretion was studied in 21 patients (case nos. 1 - 9, 11 - 19 and 21 - 23 in Table XII). In patients 17 and 22 plasma lignocaine and its metabolites only were estimated. The study was performed as previously described for healthy subjects (pages 46,47) except that blood samples were taken at 2, 4, 6, 8, 12 and 24 hours after drug ingestion.

2. Results:

1. Plasma

a. Plasma lignocaine concentrations

The plasma lignocaine concentrations in the individual patients at the different sampling times are shown in Table XXII compared with the mean values for healthy subjects. The patients have, as previously described, been divided into 3 groups on the basis of their prothrombin time ratio and serum albumin concentrations. The 2 patients (nos. 6 and 8) who had previously undergone a lieno-renal shunt were included in group 3 as their plasma lignocaine concentrations and plasma half-lives were similar to patients in that group.

The mean (± SEM) plasma lignocaine concentrations in the 3 groups of patients and in healthy subjects are shown in Fig. 8. In all but one patient (no. 23) the highest lignocaine concentration occurred 2hrs after ingestion. At the time of the initial sample (2 hrs) the mean plasma lignocaine concentration was 0.67 µg/ml in group 1, 0.75 µg/ml in group 2 and 1.55 µg/ml in group 3 - compared with a value of 0.44 µg/ml in healthy subjects.

At all sampling times patients in group 3 had significantly higher plasma lignocaine concentrations than group 1 ($p < 0.02$), group 2 ($p < 0.05$) and healthy subjects ($p < 0.01$). The initial mean lignocaine concentration in those with severe liver disease (group 3) was 3.5 times that in healthy subjects whilst at 4, 6, 8 and 12 hrs the ratios were 7.2, 14,5, 21 and 61 respectively. There was no significant difference in the plasma concentrations between groups 1 and 2 or between both these groups and the concentrations in healthy subjects at any of the sampling times except at 4 hrs where group 2 had significantly higher concentrations than the healthy subjects.

In all the patients the highest plasma lignocaine concentration (2.69 µg/ml at 2 hrs.) was seen in patient no. 8 who had previously undergone a lieno-renal shunt.

At the time of the 24 hour sample 4 of the 6 patients in group 1 and 1 of the patients in group 2 had no detectable lignocaine in the plasma (lower limit of assay 0.01 µg/ml). All patients in group 3 had detectable lignocaine concentrations at that time. (In healthy subjects, no subject had detectable lignocaine in the plasma at 24 hours).

There was a significant correlation between the 2 hour plasma lignocaine concentration and the serum albumin ($r = -0.50$; $p < 0.05$) but not with the P.T.R. ($r = 0.18$; $p > 0.1$) or the patient's weight ($r = 0.12$; $p > 0.1$).

b. Plasma lignocaine half-life

The plasma lignocaine half-life values for each patient are shown in Table XXII compared with the mean values in healthy subjects.

The plasma half-life was calculated from the plasma concentrations over the period 2 - 12 hours.

The mean plasma lignocaine half-life in group 1 was 3.71 hours (range 1.8 to 7.5 hours), in group 2, 3.0 hours (range 2.1 to 4.1 hours) and in group 3, 9.46 hours (range 4.5 to 19.0 hours).

The half-lives in group 1 and group 2 were significantly shorter than those of group 3 ($p < 0.02$ and $p < 0.025$ respectively). There were, however, no significant differences between the half-life values of groups 1 and 2 ($p = 0.06$). All 3 groups of patients had statistically significantly prolonged half-lives in comparison with those observed in healthy subjects, (group 1 and healthy subjects $p < 0.025$; group 2 $p > 0.005$; and group 3 $p < 0.001$).

In group 1 2 of the 7 (27%) patients had lignocaine half-lives outwith the range seen in healthy subjects, in group 2, 1 in 4 of the patients whilst in group 3 all patients had abnormally prolonged half-lives.

Taking all the patients together ($n = 21$) there was a significant correlation between the peak lignocaine concentration and the lignocaine half-life value ($r = 0.49$; $p < 0.05$). If the two patients who had previously undergone a porto-systemic shunt are excluded (i.e. $n = 19$) the correlation becomes more significant ($r = 0.61$, $p < 0.01$).

Overall there were significant correlations between the plasma lignocaine half-life values and the plasma albumin ($r = -0.70$; $p < 0.001$) and P.T.R. ($r = 0.78$; $p < 0.001$) but not with serum bilirubin ($r = 0.09$; $p > 0.1$), A.L.T. ($r = 0.02$; $p > 0.1$) and alkaline phosphatase ($r = 0.04$; $p > 0.1$).

TABLE XXII

PLASMA LIGNOCAINE CONCENTRATIONS (µg/ml) AND HALF-LIFE VALUES (HOURS) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 400 mg. OF LIGNOCAINE HYDROCHLORIDE ORALLY.

		HOURS AFTER INGESTION						HALF-LIFE
	PATIENT NO.	2	4	6	8	12	24	(HOURS)
GROUP 1	1	0.43	0.17	0.11	0.07	-	-	2.3
	2	0.66	0.20	0.13	0.06	0.03	0	1.8
	3	0.28	0.06	0.04	0.03	0.02	0.02	4.3
	4	0.69	0.26	0.11	0.06	0.02	0	1.8
	5	0.45	0.31	0.16	0.09	0.06	0.02	4.6
	7	1.52	1.47	0.86	0.50	0.47	0.16	7.5
	MEAN	0.67	0.41	0.23	0.13	0.11	0.06	3.71
	S.D.	0.44	0.52	0.30	0.17	0.19	0.08	2.22
GROUP 2	9	0.37	0.15	0.09	0.05	-	-	2.6
	11	0.63	0.45	0.16	0.16	0.12	0.03	4.1
	12	0.39	0.20	0.09	0.05	0.01	0	2.1
	13	1.63	1.25	0.82	0.58	-	-	3.2
	MEAN	0.75	0.51	0.29	0.20	0.07	-	3.00
	S.D.	0.59	0.50	0.35	0.25	0.07	-	0.86
GROUP 3	6	1.14	0.72	0.39	0.39	0.36	0.07	6.1
	8	2.69	2.71	2.68	1.47	0.94	0.20	5.0
	14	1.13	0.82	0.60	0.48	0.23	0.08	4.5
	15	0.98	0.70	0.71	0.60	0.41	0.19	9.0
	16	0.97	0.55	0.34	0.31	0.23	0.07	5.6
	17	2.27	1.65	1.30	1.03	0.73	0.25	7.1
	18	1.09	0.82	0.74	0.63	0.47	0.08	6.0
	19	2.31	2.03	1.55	1.30	0.51	0.51	12.4
	21	2.09	1.47	1.18	1.02	0.85	0.46	13.2
	22	1.75	1.57	1.71	1.61	1.40	0.80	16.2
	23	0.70	1.17	1.12	1.08	-	-	19.0
	MEAN	1.55	1.29	1.20	0.90	0.61	0.27	9.46
	S.D.	0.68	0.70	0.69	0.45	0.40	0.24	4.97
HEALTHY SUBJECTS	MEAN	0.44	0.18	0.08	0.043	0.01	0	1.74
	S.D.	0.17	0.09	0.05	0.022	-	-	0.28

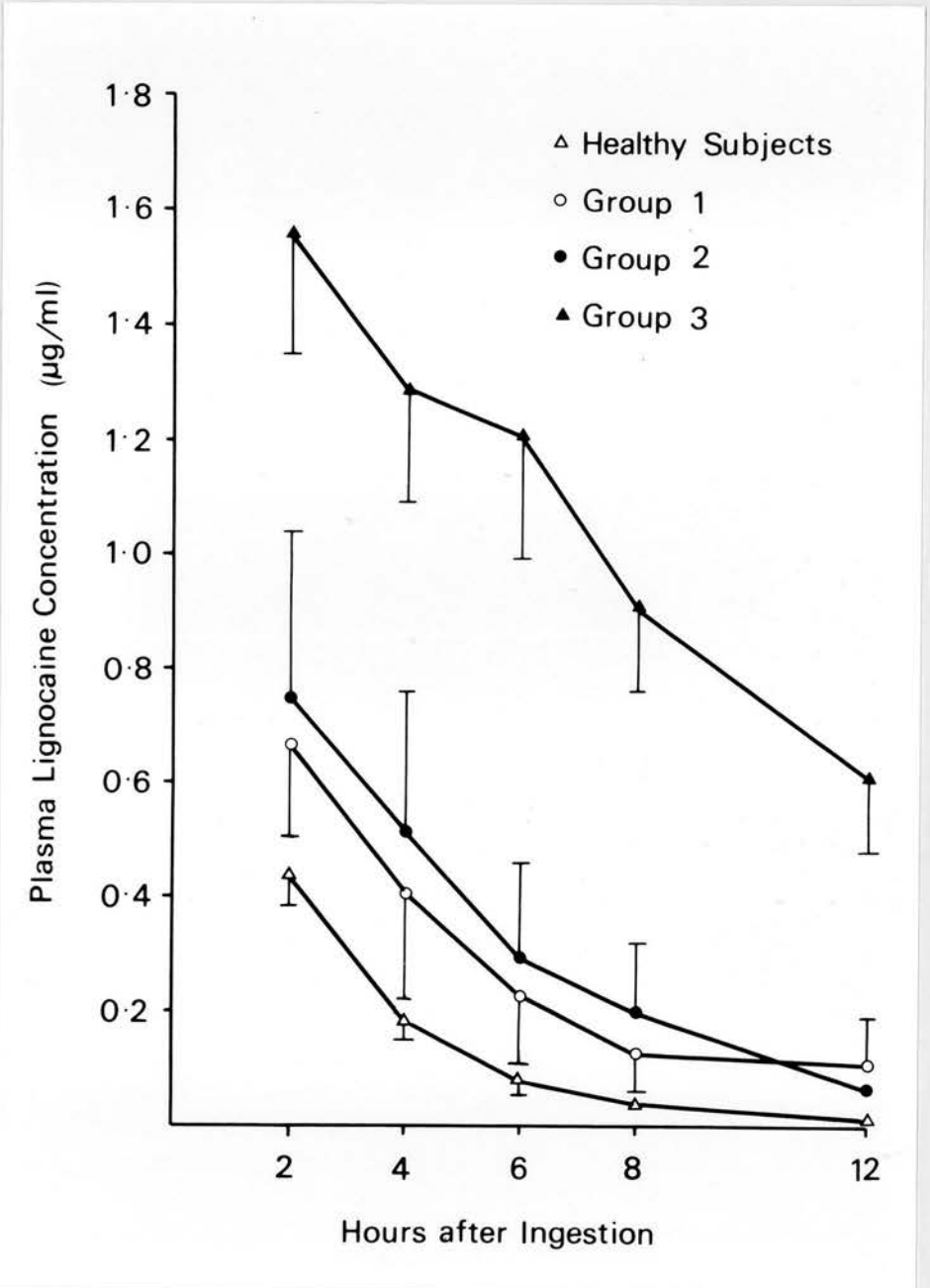

Fig. 8

Plasma lignocaine concentrations in healthy subjects and 3 groups of patients with different severity of chronic liver disease after a single oral dose of 400 mg. (mean ± S.E.M.)

c. Plasma EGX concentrations

The individual EGX concentrations in the patients at the different sampling times are shown in Table XXIII, in comparison with the mean values in healthy subjects. The mean values in the 3 groups of patients and those in normal subjects are shown in Fig. 9.

In group 1 the peak plasma EGX concentration occurred 2 hrs after lignocaine ingestion in 5 of the 6 patients. In group 2 the peak concentration in all 4 patients was at 2 hrs. whilst in group 3 only 2 of the 11 patients had maximal plasma concentrations at that time. Of the other patients in group 3 the maximal plasma concentration occurred at 4 hrs, in 4, 6 hrs in 3, and in the remaining patient the peak concentration was delayed until 12 hrs after ingestion.

At the time of the 24 hour sample 4 of 6 patients in group 1, 1 of 2 in group 2 and 10 of 11 patients in group 3 had detectable amounts of EGX in the plasma (lower limit of assay 0.01 µg/ml). In healthy subjects only 1 of 6 subjects had detectable amounts of EGX at 24 hours.

Although at the time of the initial sample group 3 had a lower mean plasma EGX concentration than the other two groups there were no significant differences in the plasma concentrations between group 1 (mean concentration 0.31 µg/ml), group 2 (0.34 µg/ml) and group 3 (0.23 µg/ml).

There were no significant differences between the plasma concentrations in the three groups of patients at any of the other sampling times apart from at 6 and 8 hours when group 3 had significantly higher concentrations than group 1 ($p < 0.05$). The mean concentrations in groups 2 and 3 became higher than in group 1 by 4 hours suggesting delayed production of EGX.

In comparison with the EGX concentrations observed in healthy subjects group 1 had significantly lower levels at 2 and 4 hours only ($p < 0.025$) and groups 2 and 3 at 2 hrs only ($p < 0.05$).

Therewere no significant differences at any of the other sampling times ($p > 0.05$).

d. Apparent EGX plasma half-lives

The apparent plasma half-life values for each patient are shown in Table XXIII compared with the mean values in healthy subjects.

The mean plasma EGX half-life in group 1 was 3.57 hours (range 2.13 to 6.78 hours); in group 2, 5.21 hours (range 2.93 to 8.04 hours) and in group 3, 12.70 hours (range 3.32 to 32.26 hours). The plasma half-life in group 1 was not significantly different from that of group 2. Group 3, however, had a significantly longer half-life than group 1 ($p < 0.001$). There was no significant difference in the half-life values between groups 2 and 3.

In comparison with the EGX half-lives observed in healthy subjects (2.16 hrs) groups 2 and 3 had significantly prolonged half-lives ($p < 0.01$) group 1 not being significantly different ($p > 0.1$).

In the patients overall there was a significant correlation between the peak plasma lignocaine concentrations and the EGX half-lives ($r = -0.55$ $p < 0.01$). A significant correlation was also observed between the lignocaine and EGX half-lives ($r = 0.75$, $p < 0.001$) and between the EGX half-life and the serum albumin ($r = -0.63$; $p < 0.01$) and the P.T.R. ($r = 0.76$; $p < 0.001$).

TABLE XXIII

PLASMA CONCENTRATIONS OF EGX (μg/ml) AND APPARENT HALF-LIFE VALUES (HOURS) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 400 mg. OF LIGNOCAINE HYDROCHLORIDE ORALLY.

	PATIENT NO.	HOURS AFTER INGESTION						APPARENT HALF-LIFE (HOURS)
		2	4	6	8	12	24	
GROUP 1	1	0.47	0.22	0.13	0.09	-	-	2.55
	2	0.33	0.18	0.10	0.05	0.040	0	2.13
	3	0.31	0.12	0.06	0.07	0.042	0.016	5.28
	4	0.46	0.24	0.12	0.10	0.028	0	2.56
	5	0.19	0.18	0.09	0.05	0.050	0.030	2.16
	7	0.15	0.34	0.20	0.20	0.150	0.080	6.78
	MEAN	0.31	0.21	0.11	0.09	0.06	0.02	3.57
	S.D.	0.13	0.07	0.04	0.05	0.04	0.03	1.96
GROUP 2	9	0.23	0.16	0.08	0.06	-	-	2.93
	11	0.56	0.34	0.28	0.22	0.15	0.04	6.72
	12	0.36	0.22	0.12	0.09	0.04	0	3.16
	13	0.24	0.24	0.17	0.29	-	-	8.04
	MEAN	0.34	0.24	0.16	0.14	0.10	0.02	5.21
	S.D.	0.15	0.07	0.08	0.07			2.56
GROUP 3	6	0.51	0.79	0.43	-	0.38	0.11	7.77
	8	0.34	0.49	0.56	0.31	0.16	0.07	3.42
	14	0.19	0.27	0.15	0.18	0.13	0.05	8.67
	15	0.19	0.22	0.16	0.15	0.11	0.12	8.00
	16	0.24	0.21	0.18	0.15	0.11	0.09	8.52
	17	0.11	0.11	0.11	0.09	0.10	0.07	27.55
	18	0.28	0.50	0.28	0.20	0.09	0	3.32
	19	0.11	0.23	0.27	0.28	0.31	0.14	10.46
	21	0.21	0.21	0.19	0.21	0.18	0.11	17.09
	22	0.12	0.12	0.19	0.19	0.22	0.17	32.26
	23	0.23	0.24	0.38	0.29	-	-	-
	MEAN	0.23	0.30	0.25	0.20	0.17	0.09	12.70
	S.D.	0.11	0.20	0.14	0.06	0.09	0.04	9.89
HEALTHY SUBJECTS	MEAN	0.75	0.37	0.21	0.11	0.04	0.01	2.16
	S.D.	0.31	0.16	0.16	0.10	0.05		0.77

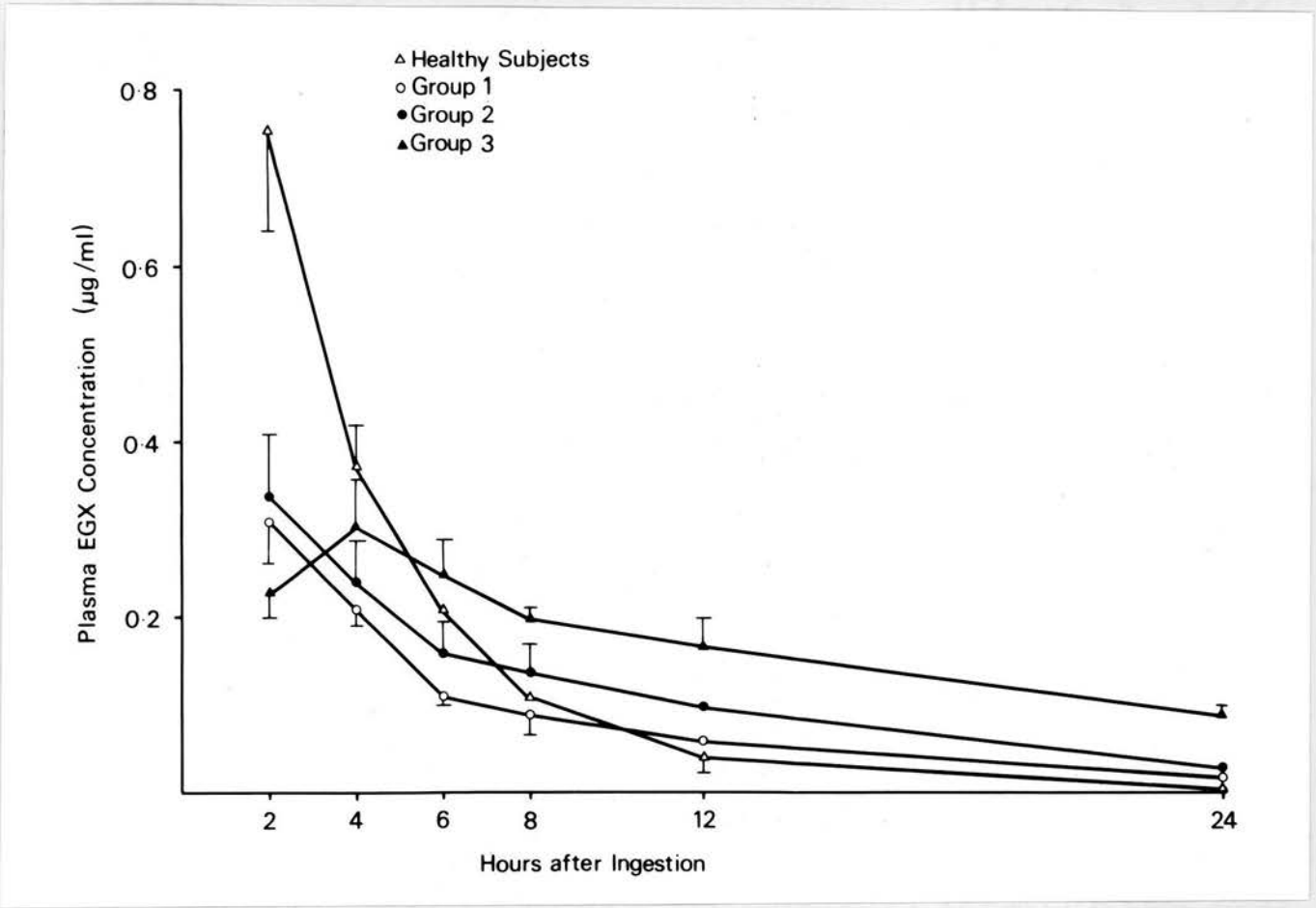

Fig. 9

Plasma ethylglycylxylidide (EGX) concentrations in healthy subjects and 3 groups of patients with different severity of chronic liver disease after a single oral dose of 400 mg. of lignocaine hydrochloride. (mean ± S.E.M.)

e. Plasma GX concentrations

The plasma GX concentrations in the individual patients at the different sampling times are shown in Table XXIV, compared with the mean values in healthy subjects.

In group 1 one patient in 6 and in group 2 two patients in 4 had no GX detectable in their plasma at any of the sampling times, (lower limit of assay 0.03 µg/ml). In group 3, only one on the 11 patients (case no. 6) had detectable amounts of GX in the plasma at any of the sampling times. All the healthy subjects had detectable concentrations of GX.

In group 1 the maximal plasma concentration in the 5 patients with detectable GX in the plasma was at 2 hours in 3 patients, 4 hours in 1 patient and 8 hours in 1 patient. In group 2 maximal plasma concentrations in the 3 patients with detectable plasma concentrations were seen at 4, 8 and 24 hours respectively after ingestion.

In group 1 the mean peak plasma concentration (0.11 µg/ml) occurred at 2, 4, 6 and 8 hours, whilst in group 2 the peak concentration (0.18 µg/ml occurred at 8 hours. The peak concentrations in group 1 and in group 2 were not significantly different from each other or from the peak concentrations seen in healthy subjects (0.19 µg/ml) ($p > 0.05$).

TABLE XXIV

PLASMA CONCENTRATIONS OF GX (µg/ml) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 400 mg. OF LIGNOCAINE HYDROCHLORIDE ORALLY

		HOURS AFTER INGESTION					
	PATIENT NO.	2	4	6	8	12	24
GROUP 1	1	0.19	0.16	0.19	0.14	-	-
	2	0.07	0.07	0.07	0.05	0.036	0.030
	3	0.21	0.17	0.18	0.17	0.127	0.046
	4	0.15	0.16	0.14	0.21	0.090	0
	5	0	0	0	0	0	0
	7	0.09	0.12	0.09	0.9	0.110	0.110
	MEAN	0.11	0.11	0.11	0.11	0.07	0.03
	S.D.	0.07	0.06	0.07	0.07	0.05	0.04
GROUP 2	9	0	0	0	0	0	0
	11	0.047	0.04	0.06	0.04	0.044	0.053
	12	0.105	0.13	0.10	0.11	0.115	0.060
	13	0	0.08	0.09	0.32	0.-	-
	MEAN	0.07	0.06	0.06	0.18	0.08	0.04
	S.D.						
HEALTHY SUBJECTS	MEAN	0.17	0.19	0.15	0.14	0.13	0.03
	S.D.	0.07	0.07	0.06	0.05	0.05	0.03

In Group 3 - only one patient (no. 6) had detectable GX in the plasma at any of the sampling times.

(lower limit of assay 0.03 µg/ml)

2. Urinary Excretion of lignocaine and Metabolites

The total amounts of unchanged lignocaine, EGX,GX and 4-hydroxyxylidine excreted by the individual patients in the 48 hours after the ingestion of lignocaine, the volume of urine passed in that period and the mean urinary pH are shown in Table XXV. Table XXVI shows the 48-hour excretion of these compounds in the 3 groups of patients and in healthy subjects expressed as a percentage of the ingested dose of lignocaine.

There were no significant differences between the 3 groups of patients with regard to the total amount of unchanged lignocaine, EGX, 4-hydroxyxylidine, volume of urine excreted or the mean pH of the urine. With regard to GX there was no significant difference in the total excreted between groups 1 and 2 ($p = 0.5$). However, group 3 excreted significantly less GX than group 1 ($p < 0.05$) or group 2 ($p < 0.01$).

In comparison with the excretion of lignocaine and its metabolites observed in healthy subjects groups 2 and 3 excreted more unchanged lignocaine - group 1 not being significantly different.

EGX excretion was lower in group 1 than in healthy subjects; groups 2 and 3 not being significantly different.

All 3 groups of patients however, excreted significantly less GX and 4-OH xylidine whilst the total excretion of lignocaine and its metabolites in all groups was approximately half of that observed in the healthy subjects. There was no significant difference in the mean urinary pH between any of the groups of patients and the healthy subjects.

TABLE XXV

48 hr. URINARY RECOVERY OF LIGNOCAINE, EGX, GX AND 4-oH XYLIDINE (mg) IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 400 mg. OF LIGNOCAINE HYDROCHLORIDE ORALLY.

	PATIENT NO.	LIGNOCAINE	EGX	GX	4-oH XYLIDINE	VOL. ml	pH
GROUP 1	1	24.2	17.3	6.23	63.66	-	5.50
	2	6.61	7.79	4.15	55.82	5604	5.44
	3	1.65	9.06	10.12	62.24	2200	5.87
	4	1.11	5.51	3.75	21.37	2932	6.9
	5	1.92	4.41	4.69	137.33	3556	6.45
	7	5.70	9.62	0.88	64.29	2114	5.57
	MEAN	6.86	8.94	4.97	67.45	3281	5.95
	S.D.	8.79	4.56	3.06	37.92	1425	0.59
GROUP 2	9	6.92	7.96	6.57	81.66	-	6.8
	11	23.32	36.86	5.87	20.4	3394	6.14
	12	1.60	9.66	7.78	76.58	3027	6.44
	13	14.38	14.71	5.11	52.74	3650	6.38
	MEAN	11.55	17.29	6.33	57.84	3357	6.44
	S.D.	9.43	13.35	1.13	27.96	313	0.27
GROUP 3	6	2.24	9.33	5.37	34.40	2056	6.54
	8	5.33	13.88	3.21	120.46	7305	6.96
	14	14.07	10.55	2.25	35.39	3518	6.00
	15	11.20	8.47	0.79	32.11	2623	6.14
	16	11.00	12.28	0.74	96.61	3215	5.81
	18	11.45	28.51	4.11	46.69	4372	6.52
	19	2.15	5.93	0.58	32.59	622	6.30
	21	14.46	20.20	0.71	15.24	1926	6.07
	23	27.68	33.56	1.04	30.45	-	7.10
	MEAN	11.06	15.85	2.08	49.32	3204	6.38
	S.D.	7.80	9.57	1.76	35.02	2008	0.43
HEALTHY* SUBJECTS	MEAN	2.84	14.53	21.45	117.0	-	6.18
	S.D.	0.62	1.94	4.15	9.34	-	0.37

* From Adjepon-Yamoah (1973)

TABLE XXVI

48 HOUR URINARY RECOVERY OF LIGNOCAINE, EGX, GX AND 4-oH XYLIDINE (AS % OF DOSE) IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 400 mg. OF LIGNOCAINE HYDROCHLORIDE ORALLY.

VALUES ARE MEANS + S.D.

	LIGNOCAINE	EGX	GX	4-oH XYLIDINE	TOTAL EXCRETION	URINARY pH
*HEALTHY SUBJECTS (n=7)	0.82 ± 0.48	4.2 ± 1.6	6.2 ± 3.2	33.8 ± 7.2	46.2 ± 8.7	6.18
GROUP 1 (n=6)	1.98 ± 2.5	2.6 ± 1.3	1.4 ± 0.9	19.5 ± 11.0	25.5 ± 11.3	5.95
GROUP 2 (n=4)	3.34 ± 2.7	5.0 ± 3.8	1.8 ± 0.3	16.7 ± 8.1	26.9 ± 2.3	6.44
GROUP 3 (n=9)	3.19 ± 2.3	4.6 ± 2.8	0.6 ± 0.5	14.3 ± 8.3	22.6 ± 8.4	6.38

* FROM ADJEPON-YAMOAH (1973)

3. DISCUSSION

There has apparently been onlyone previous study of the metabolism of lignocaine in patients with chronic liver disease (Thomson et al., 1973). In that study, in patients with alcohol induced liver disease, the mean plasma half-life in the patients (296 minutes) was significantly prolonged compared with that in normal subjects (mean 98 minutes). Plasma metabolites and patterns of urinary excretion were not studied.

In this present study lignocaine absorption appeared to be rapid - in only one patient was the peak plasma concentration not reached two hours after ingestion. Although the mean maximum plasma lignocaine concentration in those patients with less severe liver disease (groups 1 and 2) was 1.5 and 1.7 times greater than the mean concentration in healthy subjects this was not a statistically significant difference. However, in those patients with severe liver disease (group 3) the maximum concentration was 3.5 times higher than the healthy subjects; 7 of the 11 patients having concentrations in the therapeutic range of 1.5 - 4.0 µg/ml. In this group the plasma lignocaine concentrations at the different sampling times were 3.5 to 61 times greater than those of healthy subjects. In the patients overall, there was a significant correlation between the 2 hour plasma lignocaine concentration and the serum albumin only.

This higher initial plasma lignocaine concentration in patients is probably mainly due to a greatly reduced first pass metabolism secondary to intra - and/or extra hepatic shunting, although impaired drug metabolising enzyme activity may also be partly responsible. Support for this explanation is provided by the observation that the highest initial plasma lignocaine concentration (2.69 µg/ml) was seen in case number 8 with a slightly low serum albumin but normal P.T.R. who had previously undergone a porto-systemic shunt.

The plasma lignocaine half-life was correlated with the severity of the liver disease; it being more prolonged the lower the serum albumin or higher the P.T.R. There was, however, no correlation with the serum bilirubin, A.L.T. or alkaline phosphatase. This finding is at variance with those of Thomson et al., (1973) who found no correlation between any of the routine liver function tests and either the plasma half-life or plasma clearance of lignocaine. Even in patients with mild liver disease (groups 1 and 2) 6 of the 10 patients had half-life values outwith the range in healthy subjects, whilst in those with severe disease all 11 patients had abnormal half-lives; the mean value being more than 5 times that seen in healthy subjects. The patients (mean age 49 years) were slightly older than the healthy subjects (mean age 29 years). Although Nation, Triggs and Selig (1977) have noted the plasma half-life to be longer in elderly than younger subjects it is unlikely that age alone could account for more than a small percentage of the differences observed.

Although lignocaine metabolism is depressed in cardiac failure (Thomson et al., 1973; Prescott, Adjepon-Yamoah & Talbot, 1976) none of these patients in the study was in cardiac failure. In contrast with the healthy subjects in the patients overall there was a significant correlation between the peak plasma lignocaine concentration and the plasma lignocaine half-life.

The initial mean EGX plasma concentrations were significantly lower in all the groups of patients than in the healthy subjects. Eight hours after ingestion, however, the mean concentrations in the patients were higher than in the healthy subjects reflecting the delayed production of EGX. Indeed it was noted that the more severe the liver disease the greater was the delay in reaching peak plasma EGX concentrations There was a correlation between the peak plasma lignocaine concentration and the apparent half-life of EGX suggesting that lignocaine may be /

be competing with EGX for the same enzymes. The more severe the liver disease the more prolonged was the EGX half-life and indeed correlations were demonstrated between the EGX half-lives and the serum albumin and P.T.R. There was also a correlation between the plasma lignocaine and EGX half-lives.

A similar pattern was seen with GX. As the liver disease increased in severity the plasma concentrations of GX decreased and the delay before peak plasma concentrations were attained became longer. Thus in contrast with healthy subjects who all had detectable plasma concentrations of GX; in group 1, 1 in 7 and in group 2, 2 of 4 patients had no detectable GX in the plasma whilst in group 3 GX was detected in only one of 11 patients at any of the sampling times. The reduced and delayed formation of GX may again reflect competition by abnormally high concentrations of lignocaine with EGX for the drug metabolising enzymes.

The total amount of lignocaine and its metabolites excreted in the 48 hours following lignocaine ingestion was significantly lower in all 3 groups of patients than in healthy subjects. The excretion reflects the plasma concentrations. Thus groups 2 and 3 excreted more unchanged lignocaine and all 3 groups less GX and 4-oH oxylidine than healthy subjects. Although plasma concentrations of EGX were lower in patients with severe liver disease, urinary excretion over 48 hours was similar to that of healthy subjects. It might be expected, however, that in the first few hours after drug administration, EGX excretion in this group would be lower than in healthy subjects.

These differences in excretion are unlikely to be due to impaired renal function as the plasma urea was raised in one patient only (no. 23) in whom total excretion was similar to other patients. Although renal clearance of lignocaine, EGX, and GX is pH-dependent (Eriksson and Granberg, 1965; Mather and Thomas, 1972) there were no significant differences in the mean urinary pH between the healthy subjects and any of the groups of patients. This, therefore, cannot explain the differences/

differences observed. As total excretion is not related to urine volume (Adjepon-Yamoah, 1973), this also cannot explain the observed differences in total excretion between the 3 groups of patients and the healthy subjects. These observed differences are therefore probably due largely to the reduced formation of metabolites.

4. SUMMARY

The plasma concentrations and 48-hour urinary excretion of lignocaine and its metabolites were measured in 21 patients with chronic liver disease following 400 mg. of lignocaine hydrochloride orally. At the time of the initial venous sample (2 hours) those patients with an abnormal serum albumin and P.T.R. had significantly higher plasma lignocaine concentrations (mean 1.55 µg/ml) than those patients where one (mean 0.75 µg/ml) or both of these indices was normal (0.67 µg/ml) or in healthy subjects (0.44 µg/ml).

The plasma lignocaine half-lives in those patients with an abnormal serum albumin and P.T.R. (9.46 ± 5.0 hours) was significantly greater than those patients where one (3.0 ± 0.9 hours) or both of these indices was normal (3.7 ± 2.2 hours). The lignocaine half-life was related to a reduced albumin and prolonged P.T.R.

The initial mean plasma EGX concentrations were significantly lower in all 3 groups of patients than in healthy subjects. There was also a correlation between the plasma EGX half-lives and the serum albumin and P.T.R. A correlation was also noted between the plasma lignocaine and EGX half-lives.

As the severity of the liver disease increased the plasma concentrations of GX decreased and the delay before peak plasma concentrations were attained became longer. Of the 11 patients with severe liver disease, only 1 had detectable plasma concentrations.

The total urinary excretion of lignocaine and its metabolites in all 3 groups of patients was only half of that in healthy subjects. The more severe the disease the more unchanged lignocaine and the less GX and 4-oH xylidine was excreted.

CHAPTER 7

COMPARATIVE METABOLISM OF PARACETAMOL, ANTIPYRINE AND LIGNOCAINE IN PATIENTS WITH CHRONIC LIVER DISEASE

In the previous 3 chapters the metabolism of paracetamol, antipyrine and lignocaine was described in patients with chronic liver disease. One of the main aims of these studies, however, was to compare and contrast the metabolism of these drugs in such patients with reference to their metabolism in healthy subjects. To this end the metabolism of these drugs was studied consecutively over a period of 7 - 10 days. Paracetamol, antipyrine and lignocaine metabolism was studied in 16, 19 and 21 patients respectively. The metabolism of all 3 drugs was studied in 15 patients whilst at least two drugs were studied in 21 patients.

1. Plasma drug concentrations

a. Results

The mean plasma concentrations of the 3 drugs at the time of the initial venous sample in the 3 groups of patients compared with the corresponding mean concentrations observed in healthy subjects are shown in Table XXVII. It can be seen that for paracetamol and lignocaine the percentage increase in the mean plasma concentration over that seen in healthy subjects becomes greater as the severity of the liver disease - as judged by the serum albumin and P.T.R. - increases. Thus with paracetamol the mean percentage changes were -16, +9 and +80% in groups 1, 2 and 3; the corresponding figures for lignocaine being much greater at 52, 70 and 252%. With antipyrine, however, there was little difference between the 3 groups of patients the increases being 24, 22 and 35% respectively.

There were significant correlations between the initial plasma concentrations of lignocaine and the serum albumin only ($r = -0.47$; $p < 0.05$) and between paracetamol and the serum albumin ($r = -0.69$; $p < 0.01$)/

and the P.T.R. ($r = 0.68$; $p < 0.01$). No such correlations were observed with antipyrine. There were no statistically significant correlations between the initial plasma concentrations of any of the 3 drugs and any of the other liver function tests or the patients' age or weight.

TABLE XXVII

MEAN PLASMA DRUG CONCENTRATIONS (μg/ml) AT TIME OF INITIAL SAMPLE IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE

The % Change from the Mean in Healthy Subjects is shown in parenthesis

	HEALTHY SUBJECTS	PATIENTS GROUP 1	PATIENTS GROUP 2	PATIENTS GROUP 3	TIME OF INITIAL SAMPLE (HOURS)
Paracetamol	12.9	10.8 (-16%)	14.0 (9%)	23.2 (80%)	3
Antipyrine	22.3	27.7 (24%)	27.3 (22%)	30.1 (35%)	4
Lignocaine	0.44	0.67 (52%)	0.75 (70%)	1.55 (252%)	2

b. Discussion

Most studies of drug metabolism in liver disease have concentrated on the measurement of the plasma half-life or clearance of the drug, little attention bein given to the plasma drug concentrations. Yet in terms of potential drug toxicity the most important factor is the drug plasma concentration.

The plasma concentrations of the 3 drugs in this study are what might be predicted from the hepatic extraction ratios of the drugs given that as the severity of the liver disease increases the degree of porto-systemic shunting increases, and may reach 60% of the total portal blood flow (Groszman et al., 1972, Groszman et al., 1976). Thus for drugs with a low hepatic extraction ratio (e.g. antipyrine: 0.04) the proportion of the drug extracted from the plasma by a single passage through the liver is very small (4%). Hence as the severity of the liver disease increases and effective liver blood flow is reduced there should be no significant change in the amount of the drug reaching the systemic circulation.

This is seen in this study where there was no significant difference between the mean initial antipyrine plasma concentrations in the 3 groups of patients. Although all were slightly increased over the concentrations seen in healthy subjects the initial sample was 4 hours after drug ingestion and as the drug is rapidly absorbed these concentrations may perhaps reflect slower metabolism in the patients.

As paracetamol has a higher hepatic extraction ratio (0.10 - 0.20) than antipyrine it might be predicted that the mean initial plasma paracetamol concentrations in the patients compared with those in healthy subjects would be proportionally higher than with antipyrine. However, this was not seen in all 3 groups of patients in this study. In groups 1 and 2 the percentage changes were less with antipyrine; although in/

in group 3 the change was twice that with antipyrine. There are two possible explanations for these findings. Firstly the hepatic extraction ratio of paracetamol is relatively low and therefore its removal from the plasma may, like antipyrine, be little affected by changes in liver blood flow. Secondly there is some evidence in animals that paracetamol may be metabolised in the gut (Josting, Winne and Bock, 1976) and this also could,in part, account for the findings. Thus the degree of first-pass metabolism of antipyrine would appear to be unaffected by changes in the severity of the liver disease, although this study suggests that for paracetamol there is a reduction of first-pass metabolism in patients with severe liver disease.

In contrast, however, there were more marked increases in the initial plasma lignocaine concentrations compared with those of healthy subjects; the percentage increase being 52, 70 and 252 in groups 1, 2 and 3 respectively. This is what would be predicted on the basis of the high hepatic extraction ratio (0.70), as its rate of removal from the plasma is highly dependent on the effective liver blood flow. Thus as liver disease becomes more severe and porto-systemic shunting increases the degree of first pass metabolism decreases resulting in high plasma concentrations. Thus the systemic bioavailability of the drug becomes greater as the liver disease becomes more severe. In healthy subjects the systemic availability of a dose of lignocaine has been shown to be about 35% (Boyes and Kennaghan, 1971). On that basis the systemic availability of lignocaine in groups 1, 2 and 3 would be approximately 50, 60 and 120%.

The 2 hour plasma lignocaine concentration has apparently exceeded the theoretical maximum of 100%, this also having been described for labetalol by Homeida, Jackson and Roberts (1978). These authors advanced two possible explanations for this finding and it is possible that these may also explain the finding with lignocaine.

Firstly, that as the metabolism of labetalol is saturable the metabolic capacity of the liver may have been exceeded. Secondly, very high concentrations of labetalol in the hepatic vascular bed might diffuse into the biliary canaliculi and hence into the hepatic bile, resulting in recirculation after oral administration.

The validity of the concept of the hepatic extraction ratio of the drug determining its plasma concentration is strengthened by the plasma concentrations of the drugs in the patients who had previously undergone porto-systemic shunting (Table XXVIII). Thus in patient no. 6 the % increase over healthy subjects in the initial plasma antipyrine, paracetamol and lignocaine concentrations were 35, 60 and 159%, whilst in patient no. 8 the increases for antipyrine and lignocaine were 67 and 511%. Thus the shunt had less effect on the plasma concentrations of the low hepatic extraction ratio drugs and a much larger effect on the high hepatic extraction ratio drug. It must be conceded, however, that the differences in these plasma drug concentrations could, in part, be due to the reduced rate of metabolism of the drugs in these patients (Table XXXI) as the samples were taken 2 - 4 hours after drug administration.

This concept of higher plasma concentrations of drugs with a high hepatic extraction ratio in patients with chronic liver disease following oral administration has been borne out by other recent studies. Thus Branch et al., (1977) noted that in patients with chronic liver disease there was decreased first-pass metabolism of propranolol and thus increased plasma concentrations of the drug i.e. increased systemic bioavailability of the drug.

Two further studies, using other drugs with a high hepatic extraction ratio, have confirmed these findings. Thus Pentikäinen et al., (1978) noted that there was a substantial decrease in the first pass metabolism of chlormethiazole with a resultant ten fold increase in the systemic/

bioavailability of the drug, whilst Homeida, Jackson and Roberts (1978) noted a 2 fold increase in the bioavailability of labetalol in patients with chronic liver disease. In the former study there were significant correlations between the bioavailability of the drug and the P.T.R., serum bilirubin and alkaline phosphatase and in the latter study the only significant correlation was with the serum albumin. In that respect the study of Homeida, Jackson and Roberts (1978) is in agreement with the results in this study where a significant correlation was noted between the 2 hour plasma lignocaine concentration and the serum albumin.

In terms of potential drug toxicity the most important factor is the actual plasma concentration of the drug and the marked reduction in first-pass metabolism of drugs with a high hepatic extraction ratio will result in greatly increased plasma concentrations, irrespective of the rate of removal of the drug from the plasma. This concept has been borne out by the work of Pentikäiken et al., (1978) and Homeida, Jackson and Roberts (1978) who noted that although the plasma half-life of chlormethiazole (although not the plasma clearance) and labetalol were similar in patients with chronic liver disease and healthy subjects the systemic availability of the two drugs was significantly increased in the patients. Thus drug dosage must be reduced correspondingly in patients with chronic liver disease, especially in those with decompensated cirrhosis when drugs with a high hepatic extraction ratio are prescribed.

TABLE XXVIII

INITIAL PLASMA CONCENTRATIONS (µg/ml) OF ANTIPYRINE, PARACETAMOL AND LIGNOCAINE IN TWO PATIENTS WHO HAD UNDERGONE A LIENO-RENAL SHUNT IN COMPARISON WITH MEAN CONCENTRATIONS IN HEALTHY SUBJECTS

The % Change from the Mean in Healthy Subjects is shown in parenthesis.

	ANTIPYRINE	PARACETAMOL	LIGNOCAINE
Healthy Subjects	22.3	12.9	0.44
Patient no. 6	30.1 (35%)	20.6 (60%)	1.14 (159%)
Patient no. 8	37.2 (67%)	-	2.69 (511%)

2. Plasma drug half-lives

a. Results

The mean plasma half-lives of the 3 drugs in the 3 group of patients compared with the mean half-lives in the healthy subjects are shown in Table XXIX. For all 3 drugs there was little difference in the prolongation of the plasma half-lives between groups 1 and 2; group 3 having a much prolonged half-life compared with the other two groups. It can be seen that the paracetamol half-life was least affected; lignocaine being the most prolonged. Thus in patients with severe liver disease the increases in the paracetamol, antipyrine and lignocaine half-lives were 75, 341 and 444% respectively.

Fig. 10 shows the percentage frequency of abnormal plasma drug half-lives (i.e. greater than the mean $\pm$ 2 S.D. of healthy subjects) related to the serum albumin and P.T.R. Thus whilst in group 1 only 25 and 20% of patients respectively had abnormal paracetamol and antipyrine half-lives, 50% had abnormal lignocaine half-lives. A similar pattern was seen in group 2 where 75% of patients had an abnormal lignocaine half-life whilst in group 3 all patients had abnormal half-lives of all 3 drugs.

There were significant correlations between the plasma paracetamol, antipyrine and lignocaine half-lives and the serum albumin and the vitamin K_1-corrected P.T.R. (Table XXX). For all 3 drugs there was a better correlation between the plasma half-life and P.T.R. than with the serum albumin. There were no significant correlations between any of the drug half-lives and the serum bilirubin, A.L.T., alkaline phosphatase activities or the patient's age or weight.

Significant correlations were observed between the plasma half-lives of all 3 drugs: antipyrine and paracetamol ($n = 15$)($r = 0.80$, $p < 0.01$) (Fig. 11) antipyrine and lignocaine ($n = 17$)($r = 0.82$, $p < 0.01$) (Fig. 12) and paracetamol and lignocaine ($n = 14$)($r = 0.90$, $p < 0.01$)(Fig. 13).

TABLE XXIX

MEAN PLASMA PARACETAMOL, ANTIPYRINE AND LIGNOCAINE HALF-LIVES (HOURS) IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC LIVER DISEASE

The % Change from the Mean in Healthy Subjects is shown in Parenthesis.

	HEALTHY SUBJECTS	PATIENTS GROUP 1	GROUP 2	GROUP 3
Paracetamol	2.43	2.02 (-17%)	2.32 (- 5%)	4.24 (74%)
Antipyrine	11.6	16.5 (42%)	15.2 (31%)	51.1 (341%)
Lignocaine	1.74	3.71 (113%)	3.00 (72%)	9.46 (444%)

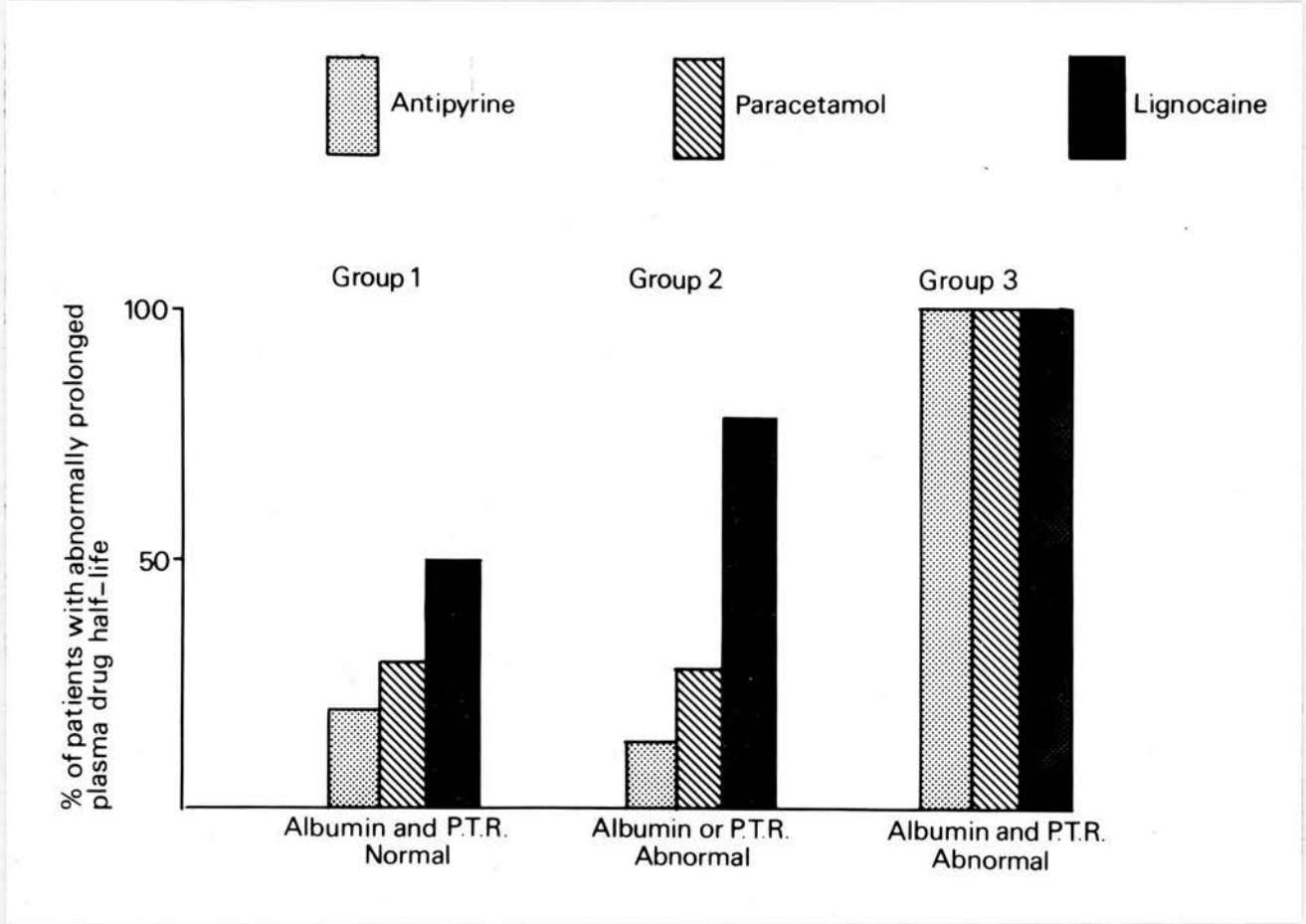

Fig. 10

Percentage of 3 groups of patients with different severity of chronic liver disease in whom the plasma half-life of antipyrine, paracetamol and lignocaine was abnormally prolonged i.e. greater than the mean +2 S.D. plasma half-life observed in healthy subjects.

TABLE XXX

CORRELATIONS (r VALUES) BETWEEN THE PLASMA PARACETAMOL, ANTIPYRINE AND LIGNOCAINE HALF-LIVES AND THE PATIENT'S LIVER FUNCTION TESTS, AGE AND WEIGHT

	SERUM ALBUMIN	P.T.R.	SERUM BILIRUBIN	A.L.T.	ALKALINE PHOSPHATASE	AGE	WEIGHT
Paracetamol half-life	-0.64	+ 0.79	0.02	0.17	0.21	0.17	0.06
Antipyrine half-life	-0.55	+ 0.91	0.13	0.14	0.10	0.25	0.10
Lignocaine half-life	-0.70	+ 0.78	0.09	0.02	0.04	0.33	0.28

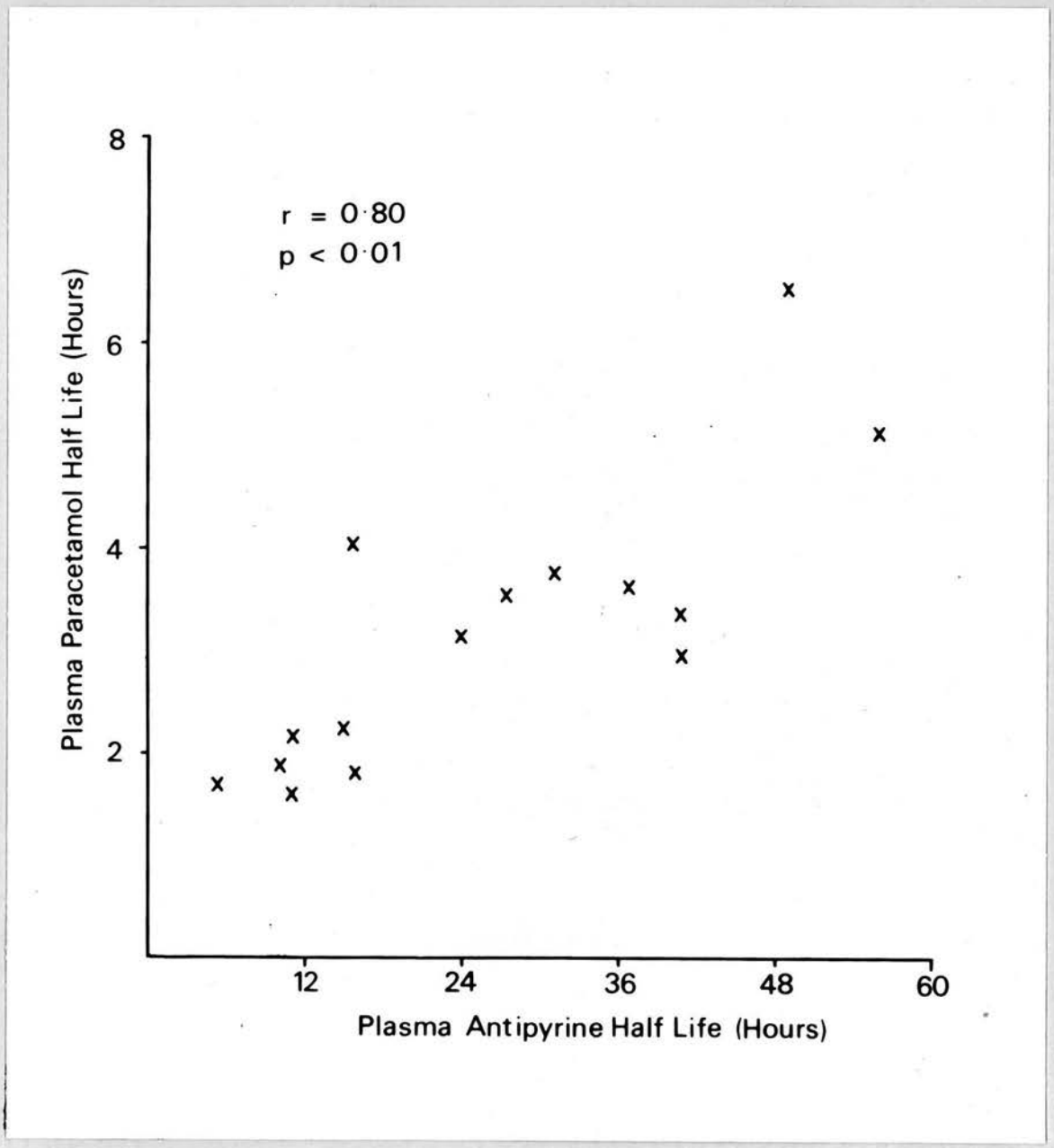

Fig. 11

Correlation between the plasma antipyrine and paracetamol half-lives in 15 patients with chronic liver disease.

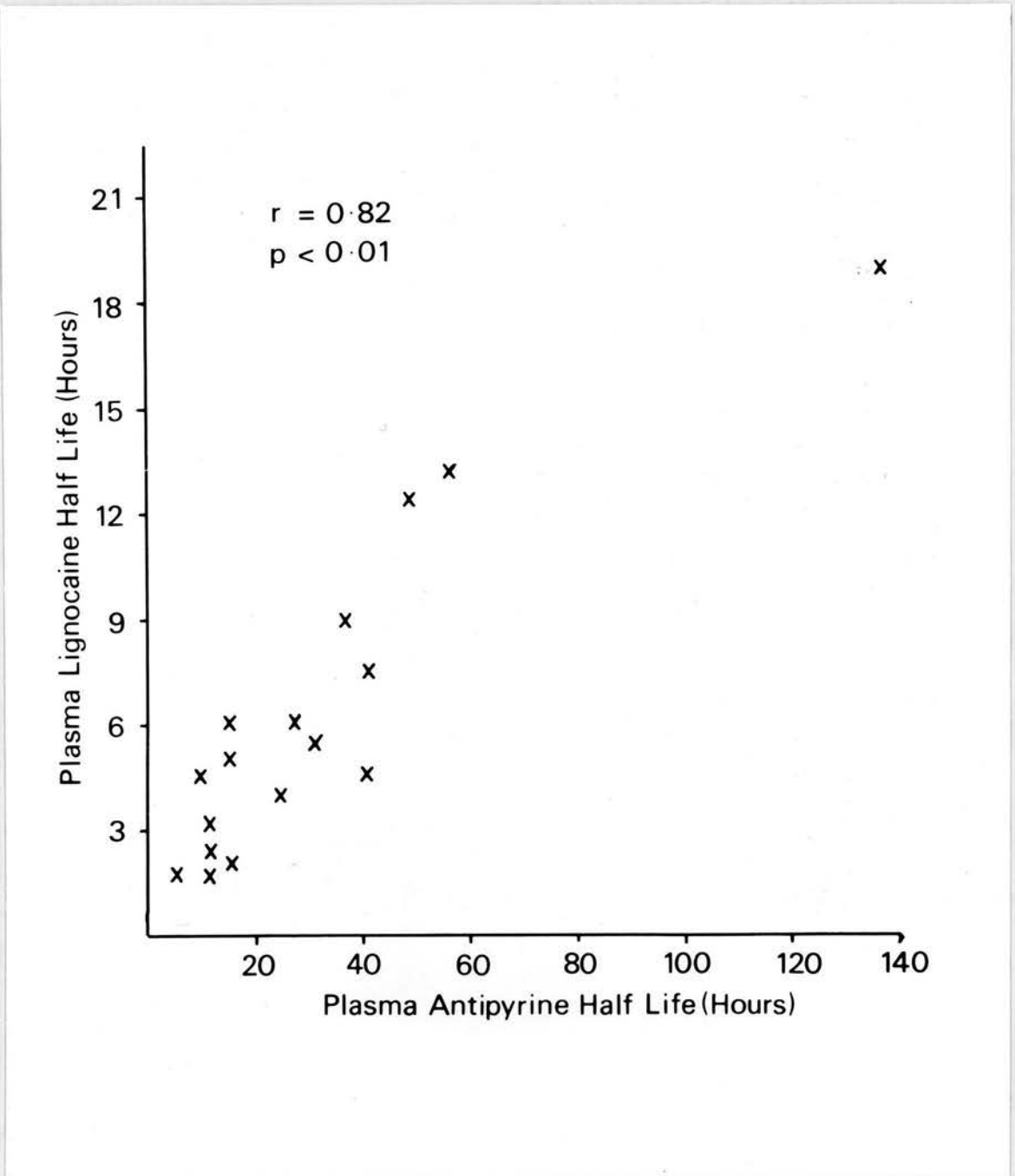

Fig. 12

Correlation between the plasma antipyrine and lignocaine half-lives in 17 patients with chronic liver disease.

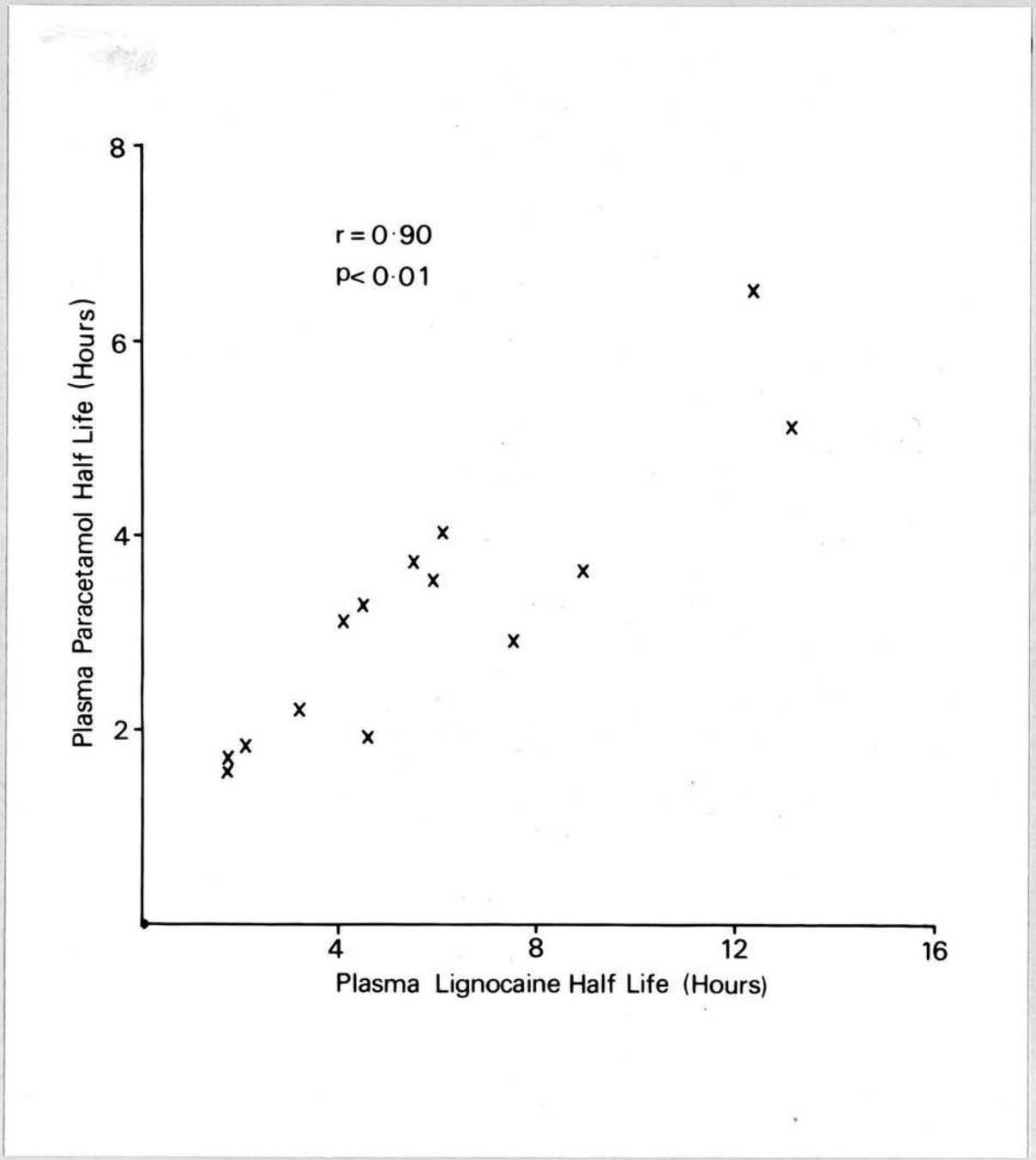

Fig. 13

Correlation between the plasma lignocaine and paracetamol half-lives in 14 patients with chronic liver disease.

b. DISCUSSION

There have been conflicting reports of the ability of patients with chronic liver disease to metabolise drugs at a normal rate. Thus the plasma half-lives of pentobarbitone (Sessions et al., 1954), aminopyrine and dicoumarol (Brodie, Burns and Weiner, 1959), antipyrine (Brodie, Burns and Weiner, 1959; Andreasen and Vesell , 1974), tolbutamide (Nelson, 1964), chloramphenicol (Held and von Olderhansen, 1971); chlorpromazine (Maxwell et al., 1972), phenylbutazone (Hvidberg, Andreasen and Ranek, 1974 and have been reported to be normal in such patients.

On the other hand the plasma half-lives or clearances of isoniazid (Levi, Sherlock and Walker; 1968), carbenicillin (Hofmann, Cestro and Bullock, 1970), lignocaine (Thomson, Rowland and Melmon; 1973), prednisone (Powell and Axelsen, 1972), amylobarbitone (Mawer, Miller and Turnberg, 1972) rifampicin (Acocella et al., 1972), antipyrine (Branch, James and Read, 1973; Andreasen et al., 1974; Branch, James and Read 1976a; Hepner et al 1977; Farrell et al., 1978), pethidine (Klotz et al., 1974); diazepam (Klotz et al., 1975); clindamycin (Avant, Schenker and Alford, 1975) have been noted to be abnormal in patients with chronic liver disease.

The results of this study with paracetamol, antipyrine, and lignocaine shown clearly that the rate of drug elimination, as evidenced by plasma half-life, becomes more abnormal relative to that of healthy subjects as the liver disease becomes more severe.

In the present studies the healthy subjects were younger than the patients. However, other studies suggest that this would not account for more than a small percentage of the differences observed. Thus Triggs et al., (1975) found only a 35% increase in the plasma paracetamol half-life in subjects with a mean age of 81 years compared with younger subjects of mean age 24 years. Based on the results of Vestal et al., (1976) the plasma antipyrine half-life in this study would be expected to be less than 10% longer in the patients than the healthy subjects/

subjects based on age differences alone. However, O'Malley et al., (1971) found the antipyrine half-life to be 45% greater in patients with a mean age of 77 years compared with healthy volunteers with a mean age of 26 years. The lack of correlation in this study between any of the plasma drug half-lives and the patients age has been confirmed by Farrell et al., (1978) who have shown that in patients with chronic liver disease there was no correlation between the antipyrine half-life and the patient's age.

In this study a correlation was demonstrated between the plasma half-life of all three drugs and the serum albumin and vitamin K_1-corrected P.T.R. This finding has now been substantiated by other workers who have demonstrated similar correlations. Thus in patients with chronic liver disease Branch, Herbert and Read (1973 & 1976a) Andreasen et al. (1974) and Farrell et al (1978) have demonstrated a significant correlation between either the plasma antipyrine half-life or the plasma clearance of antipyrine and the serum albumin and P.T.R. Similar correlations have also been demonstrated with pentobarbitone (Alvian et al., 1975) indocyanine green (Branch, James and Read, 1976a, diazepam (Branch et al 1976) and propranolol (Branch, James and Read, 1976b; Branch and Shand 1976). However, in a small number of patients with cirrhosis Hepner et al (1977) could only show a correlation between the aminopyrine and antipyrine plasma clearances and the serum albumin. No such correlations were found for diazepam or indocyanine green, whilst Klotz et al (1975) also found no correlation between the diazepam half-life and the serum albumin P.T.R. The failure of previous studies to demonstrate such significant correlations may, in part, be due to failure to adequately document the severity of the liver disease or to wait until the patients were in their optimal clinical state before commencing the investigations. However, as previously discussed, diet, alcohol and/

and cigarette consumption and previous drug administration can affect the rate of elimination of many drugs and these factors could also account for the discrepancies noted.

The finding of a lack of correlation between the plasma drug half-life of all 3 drugs and the serum bilirubin, A.L.T. and alkaline phosphatase is in agreement with other studies. Thus Branch, Herbert and Read (1973) Elfström and Lindgren (1974) and Hepner et al (1977) reported similar findings in relation to anitpyrine. In contrast, however, Farrell et al et al (1978) demonstrated a significant correlation between the antipyrine half-life and the serum bilirubin whilst Branch, Herbert and Read (1976b) demonstrated a significant correlation between (+) propranolol clearance and the serum bilirubin.

In studies on the same healthy subjects a correlation between the plasma half-lives of different drugs has not always been demonstrated. Thus although **Vesell** & Page (1968) demonstrated a correlation between the plasma half-lives of phenylbutazone and dicoumarol, and Hammar, Mårteus & Sjöqvist (1969) a correlation between the rate of metabolism of desmethylimipramine, nortriptyline and oxyphenylbutazone and Kadar et al (1973) a correlation between the half-lives of glutethimide, amobarbital and sulphinpyrazone other comparisons have not been significant. Thus **Vesell** & Page (1968c) could not demonstrate a correlation between the antipyrine half-life with that of phenylbutazone and dicoumarol, Davies & Thorgeirsson (1971) between the antipyrine and phenylbutazone half-lives and,Kadar et al (1973) between glutethimide, amylobarbitone and sulphinpyrazone half-lives and the antipyrine half-life.

In this study, however, significant correlations have been demonstrated between the plasma half-lives of all 3 drugs. In patients with chronic liver disease recent studies have also demonstrated similar correlations. Thus Andreasen et al (1974) demonstrated a correlation between the clearance of antipyrine and galactose, whilst Branch, James and Read (1976b)/

(1976) and Branch et al (1976c) demonstrated correlations between the clearances of antipyrine, indocyanine green, diazepam and d-propranolol. In addition, in a heterogenous group of patients with hepatobiliary diseases Hepner et al (1977) demonstrated weak correlations between the plasma clearances of diazepam, antipyrine and indocyanine green and between aminopyrine, antipyrine and indocyanine green but not between diazepam and aminopyrine, although in a small group of patients with cirrhosis the only positive correlation was between the aminopyrine and antipyrine clearances.

In the present study although there was a good correlation between the plasma half-lives of all three drugs, minor prolongation of the antipyrine half-life could be associated with severely impaired elimination of lignocaine and a normal paracetamol half-life. Thus the half-life of antipyrine would appear to be a poor indicator of the ability of patients with chronic liver disease to eliminate other drugs. The half-lives of paracetamol and antipyrine were increased in 20% of patients with a normal serum albumin concentration and/or P.T.R., although the mean changes over normal, of -17% and 43% respectively, are of little clinical importance in respect of drug dosages that might be prescribed. However, even when these two indices of liver function were normal the mean rate of lignocaine elimination was only 50% of normal with 50% of patients having a prolonged half-life. In contrast, the half-life of all 3 drugs was abnormal in all patients with an abnormal albumin concentration and P.T.R. Regardless of the serum albumin concentration or P.T.R., paracetamol elimination was always least affected, which might be due to conjugation of the drug at extrahepatic sites such as the gastrointestinal mucosa, which is rich in glucuronyl transferase and aryl sulphatase. (Josting, Winne & Bock, 1976).

Lignocaine elimination, in contrast, was always the most severely depressed, and in those patients with an abnormal serum albumin and P.T.R/

P.T.R. was at only 20% of the rate in healthy subjects. There are several possible explanations for this. Intrinsic hepatic blood flow is often decreased in cirrhosis by porto-systemic shunting (Groszman et al, 1972 ; and Groszman et al. 1976) and this might be expected to have a much greater effect on the clearance of drugs with a high hepatic extraction ratio such as lignocaine than on drugs with a low ratio such as paracetamol or antipyrine. Thus in cardiac failure hepatic blood flow is decreased and the plasma half-life of lignocaine greatly depressed, (Thomson et al, 1973; Prescott et al. 1976) whereas there was relatively little prolongation of the antipyrine half-life in the same patients (Prescott et al. 1976). The validity of this concept is strengthened by two other studies. Branch, Herbert & Read (1973) found no difference in the half-life of antipyrine in patients with and without evidence of porto-systemic shunting who had liver disease of similar severity suggesting that reduced liver blood flow had little effect on the clearance of antipyrine. In addition, Branch, James & Read (1976a) found that in patients with porto-systemic shunts indocyanine green clearance was more abnormal than antipyrine clearance. On the other hand Branch, James & Read (1973) demonstrated that treatment with inducing agents such as phenobarbitone greately reduced the plasma half-life of antipyrine suggesting that at least for drugs with a low hepatic extraction ratio the enzyme activity in the liver cell is a major determinant of the hepatic clearance of such drugs.

The differences observed in the half-lives of the different drugs could also be due in part to the varying activities of the different enzyme systems responsible for their metabolism. There is little information on how liver disease affects these different enzyme systems.

The findings in this study do not allow a distinction to be made between selective impairment of the different drug metabolising enzymes and reduction in intrinsic hepatic blood flow as an explanation for the observed differences in the half-lives of antipyrine, paracetamol and/

and lignocaine. For drugs with a high hepatic extraction ratio, however, liver blood flow may be more important than enzymatic activity. Support for this theory comes from the plasma half-lives of the 3 drugs in the two patients who had previously undergone a porto-systemic shunt operation (Table XXXI). It can be seen that in patient no. 6 (who had a normal serum albumin and P.T.R.) the least prolongation of the half-life compared with healthy subjects was seen with antipyrine (36%); lignocaine being most prolonged (251%) with paracetamol being intermediate (65%). This is what would be predicted on the basis of the hepatic extraction ratios of the drugs. Patient no. 8 showed a similar pattern with little prolongation in the antipyrine half-life (21%) and a much longer prolongation of the lignocaine half-life (187%).

Whatever the precise mechanisms it is clear that the elimination of some drugs is grossly abnormal in many patients with chronic liver disease. Often there may be severe depression of metabolism resulting in rapid accumulation and serious or fatal toxicity when conventional doses are used, patients with a low serum albumin concentration and a prolonged P.T.R. being most at risk. This should be borne in mind when prescribing drugs for patients with chronic liver disease. In these cases it would therefore seem appropriate to start with a reduced dosage when the drug is mainly metabolised by the liver and has a high hepatic extraction ratio.

TABLE XXXI

PLASMA PARACETAMOL, ANTIPYRINE AND LIGNOCAINE HALF-LIVES (HOURS) IN TWO PATIENTS WHO HAD UNDERGONE A LIENO-RENAL SHUNT IN COMPARISON WITH MEAN HALF-LIFE IN HEALTHY SUBJECTS

Figures in Parenthesis are the % Increase over the mean Half-life in Healthy Subjects

	Plasma half-life		
	Antipyrine	Paracetamol	Lignocaine
Healthy subjects	11.6	2.43	1.74
Patient no. 6	15.8 (36%)	4.0 (65%)	6.1 (251%)
Patient no. 8	14.0 (21%)	-	5.0 (187%)

3. SUMMARY

The simultaneous comparison of the plasma concentrations and half-lives of 3 drugs (antipyrine, paracetamol and lignocaine) with different primary routes of metabolism and different pharmacokinetic properties were studied in 23 patients with stable chronic liver disease of varying severity.

For antipyrine there was no decrease in the amount of first-pass metabolism with increasing severity of the liver disease. In the case of paracetamol there was a moderate decrease with a consequent increase in systemic bioavailability only in those patients with severe liver disease whilst with lignocaine there was an increase in the systemic bioavailability even in those patients with mild liver disease; those with severe liver disease having a marked increase. A correlation was demonstrated between the systemic bioavailability of paracetamol and the serum albumin and P.T.R. and between that of lignocaine and the serum albumin.

The half-life of paracetamol was abnormally prolonged in 9 out of 15 patients (mean 3.1 hrs., normal 2.4 hrs), of antipyrine in 10 out of 19 patients (mean 30.4 hours., normal 11.6 hrs.) and of lignocaine in 17 out of 21 patients (mean 6.6 hrs., normal 1.7 hrs.). The plasma half-lives of all 3 drugs were significantly correlated with an increase in the vitamin K_1 corrected P.T.R. and a reduction in serum albumin concentration. There was no correlation with serum bilirubin concentration or serum A.L.T. or alkaline phosphatase activities, or with the patient's age or weight. This suggests that impaired drug elimination is related to depressed protein synthesis.

There were significant correlations between the plasma half-lives of all 3 drugs, although the antipyrine half-life was a poor indicator of the ability of the patients to eliminate other drugs. The half-life of lignocaine, however, was always the most prolonged and was a highly sensitive indicator of hepatic dysfunction.

From the practical point of view the results indicate that both the pharmacokinetic characteristics of a drug as well as the severity of the liver disease should be taken into account when considering drug dosage for patients with chronic liver disease. In such patients the initial drug dosage should be reduced when the drug is mainly metabolised by the liver and has a high hepatic extraction ratio.

CHAPTER 8

METABOLISM AND EXCRETION OF PARACETAMOL IN PATIENTS WITH CHRONIC LIVER DISEASE GIVEN 1 gm. OF PARACETAMOL 8 HOURLY FOR 3 DAYS

The metabolism and excretion of paracetamol (following a single oral dose of 1500 mg.) in patients with chronic liver disease was described in Chapter 4. It was seen that paracetamol metabolism - as evidenced by its plasma half-life - was abnormally prolonged only in patients with severe liver disease. Even in these patients, however, the 24 hour urinary excretion of the mercapturate and cysteine conjugates was similar to that in control subjects. Although this would suggest that such patients have sufficient stores and/or adequate rate of synthesis of glutathione to detoxify the toxic intermediate metabolite of paracetamol it gives no insight as to whether their glutathione stores and/or rate of synthesis would be adequate to deal with repeated therapeutic doses of the drug.

The purpose of this investigation was, therefore, to study the metabolism and urinary excretion of repeated therapeutic doses of paracetamol in patients with severe liver disease in order to ascertain if it might be safe for such patients to be prescribed regular therapeutic doses of the drug.

1. Design of Study

Only patients with severe liver disease - serum albumin less than 35 gm/1 and vitamin K_1-corrected P.T.R. greater than 1.3 - were studied.

A similar pattern was followed for each patient. 1 gm. (2 tablets) of paracetamol ("Panadol") was given 8 hourly for 3 days. All tests started at 1400 hours; the last dose being given at 1400 hours on the 3rd day. In all, each patient received 10 gm. of paracetamol. Following the first dose, venous samples (10ml to lithium heparin) were obtained at 2, 4, 6 and 8 hours in order to measure the plasma half-life. Thereafter/

Thereafter venous samples were taken at 24, 48 and 72 hours (just prior to the administration of the next dose) in order to ascertain if there was anyevidence of drug accumulation. In addition, samples were obtained 1 and 2 hours after the 24 and 48 hour doses, in order to ascertain the peak concentrations reached after a further dose. Following the last dose (at 72 hours) samples were also obtained 2, 4, 6 and 8 hours later in order to again measure the plasma half-life.

All urine was collected for 96 hours; in 4 periods of 24 hours. The pH of each 24 hour collection was measured and an aliquot frozen at -20°C until assayed. Routine liver function tests and plasma urea and electrolytes were measured on the day prior to the start of the study and on the day following completion of tablet ingestion.

During the 4 days of the study the patients were permitted to eat and drink normally and no restriction was placed on their activities. Wherever possible all drugs were stopped during the study. All were hospitalised during the whole of the study.

2. Patients

The studies were carried out in 6 patients who had been admitted to hospital for treatment and/or investigation of their chronic liver disease and were undertaken when they were in their optimal clinical condition. The clinical and laboratory details of the patients studied are shown in Table XXXII. The diagnosis in cases 1, 2, 3, 5 and 6 was established by liver biopsy whilst case 4 had a liver scan typical of cirrhosis.

None of the patients was in cardiac failure although patients 2, 3 and 5 had ascites at the time of the study. None had a raised plasma urea. The following drugs had been taken regularly for some months prior to the study and were continued during the study: patient no. 1, spironolactone; no. 2, **cholestyramine** and beclomethasone; no. 3 chlormethiazole; no. 4, spironolactone and diazepam; no. 5, spironolactone,

spironolactone, cholestryramine and metoclopramide and no. 6 prednisolone and spironolactone. Patients no. 2 and 6 did not take alcohol whilst patients 1, 3 and 5 were chronic alcoholics. All had been taking 80 - 120 gm. of alcohol per day until 2 - 3 weeks prior to the study when they were admitted to hospital. Patient no. 4 had taken no alcohol in the previous year.

TABLE XXXII

CLINICAL AND LABORATORY DETAILS

PATIENT NO.	AGE:SEX	Wt. (kg)	DIAGNOSIS	BILIRUBIN (µmol/l)	ALT (units/l)	ALKALINE PHOSPHATASE (units/l)	SERUM ALBUMIN (gm/l)	PROTHROMBIN TIME RATIO
1	64:M	72	Alcoholic cirrhosis	155	25	225	26	2.0
2	62:F	55	Chronic active hepatitis	555	190	895	29	1.8
3	53:F	64	Alcoholic hepatitis	60	24	108	27	1.6
4	42:F	56	Alcoholic cirrhosis	48	12	77	32	1.6
5	60:M	70	Alcoholic cirrhosis	90	17	141	22	1.9
6	22:F	66	Chronic active hepatitis	114	58	78	28	2.2

3. Results

a. Plasma

i. Plasma paracetamol concentrations

The plasma paracetamol concentrations at 24, 48 and 72 hours (just prior to the administration of the next dose) for each of the patients are shown in Table XXXIII. There were no significant differences ($p > 0.1$) in the plasma concentrations at 24 (12.4 $\pm$ 4.2 µg/ml), 48 (12.6 $\pm$ 4.4 µg/ml) and 72 (12.2 $\pm$ 3.7) hours. In patient no. 5 there was evidence of slight accumulation at 48 hours but a much lower concentration at 72 hours suggesting that a dose had been omitted.

The peak plasma concentration following the last dose of paracetamol ranged from 17.0 to 36.2 µg/ml (mean 25.1 µg/ml).

TABLE XXXIII

PLASMA PARACETAMOL CONCENTRATIONS (μg/ml) AT 24, 48 & 72 HOURS IN PATIENTS WITH DECOMPENSATED LIVER DISEASE GIVEN 1gm PARACETAMOL 8 HOURLY FOR 3 DAYS.

PATIENT NO.	24 hr.*	48 hr.*	72 hr.*
1	14.4	16.3	16.1
2	7.7	8.0	12.9
3	16.6	15.2	13.1
4	8.1	7.7	6.0
5☆	17.3	21.6	10.0
6	15.5	16.0	12.8
Mean (n = 5)	12.4	12.6	12.2
S.D.	4.2	4.4	3.7

* plasma concentrations just prior to administration of dose

☆ omitted from calculation of means ± S.D.

ii. Plasma paracetamol half-life

The plasma paracetamol half-life in each of the patients following the first and last doses of paracetamol is shown in Table XXXIV. In patient no. 1 the half-life was measured only after the first dose.

There was no significant difference ($p > 0.1$) between the half-life following the first (5.7 $\pm$ 4.2 hours) and the last (5.1 $\pm$ 2.5 hours) dose. Patient no. 5 showed a marked reduction in the plasma half-life - from 13.2 to 9.5 hours. Even if that patient were excluded from the analysis the half-lives were still not significantly different at 3.9 $\pm$ 0.4 and 4.1 $\pm$ 0.5 hours respectively ($p > 0.1$).

iii. Liver function tests

In none of the patients did the paracetamol administration result in any changes in the serum bilirubin, A.L.T. alkaline phosphatase or P.T.R.

TABLE XXXIV

PLASMA PARACETAMOL HALF-LIFE VALUES (HOURS) FOLLOWING FIRST AND LAST DOSE OF PARACETAMOL IN PATIENTS WITH DECOMPENSATED LIVER DISEASE GIVEN 1 gm. PARACETAMOL 8 HOURLY FOR 3 DAYS

PATIENT NO.	HALF-LIFE FOLLOWING FIRST DOSE	HALF-LIFE FOLLOWING LAST DOSE
2	3.5	3.7
3	4.1	4.5
4	3.6	3.6
5	13.2	9.5
6	4.3	4.4
MEAN	5.7	5.1
S.D.	4.2	2.5

b. Urine

The urinary excretion of unchanged paracetamol and its metabolites (expressed as a % of the total daily excretion) in the four 24 hour periods is shown in Table XXXV. In patient no. 1 urine was only collected for 72 hours. In the remaining 5 patients the total recovery of unchanged paracetamol and its metabolites over the 96 hours ranged from 76 to 99% (mean 87%) of the total ingested dose.

In the 0 - 24 hour period the excretion of unchanged paracetamol and its conjugates was similar to the excretion pattern observed in healthy subjects (page 53) and patients with chronic liver disease (page 83) given a single dose of paracetamol.

Comparison of the excretion between the periods 0 - 24 and 72 - 96 hours showed there to be no significant differences ($p > 0.1$) in the excretion of unchanged paracetamol (7.0 $\pm$ 2.7% in 0 - 24 hour period and 12.4 $\pm$ 11.4% in 72 - 96 hour period), glucuronide (41.4 $\pm$ 7.2% and 45.1 $\pm$ 12.3%), sulphate (43.8 $\pm$ 6.4% and 35.9 $\pm$ 6.2%) and mercapturate (3.3 $\pm$ 2.9% and 3.0 $\pm$ 2.6%) and cysteine conjugates (4.4 $\pm$ 4.3% and 3.6 $\pm$ 4.1%).

TABLE XXXV

URINARY EXCRETION OF UNCHANGED PARACETAMOL AND ITS METABOLITES OVER 4 24 HOUR PERIODS (AS % OF TOTAL EXCRETION IN EACH PERIOD) IN PATIENTS WITH DECOMPENSATED LIVER DISEASE GIVEN 1 gm PARACETAMOL 8 HOURLY FOR 3 DAYS.

PATIENT NO.	TIME	UNCHANGED PARACETAMOL	PARACETAMOL GLUCURONIDE	PARACETAMOL SULPHATE	PARACETAMOL MERCAPTURATE CONJUGATE	PARACETAMOL CYSTEINE CONJUGATE
2		10.5	36.1	38.1	4.8	10.8
3	0-24	6.4	47.3	44.8	0.8	0.6
4	hours	5.0	51.0	41.1	1.3	1.6
5		4.1	37.5	54.3	2.1	2.1
6		9.2	35.2	40.6	7.6	7.3
MEAN		7.0	41.4	43.8	3.3	4.4
S.D.		2.7	7.2	6.4	2.9	4.3
2		11.3	37.3	33.5	6.1	11.8
3	24-48	6.0	53.3	39.5	0.6	0.5
4	hours	4.9	53.8	38.5	1.3	1.5
5		6.3	41.5	48.4	1.7	2.1
6		20.6	36.3	27.2	7.7	8.2
MEAN		9.8	44.4	37.4	3.4	4.8
S.D.		6.5	8.5	7.8	3.2	4.9
2		13.4	36.7	32.8	6.0	11.1
3	48-72	5.4	55.5	38.2	0.5	0.5
4	hours	5.3	55.8	36.7	1.1	1.1
5		5.5	44.2	46.5	1.7	2.1
6		16.0	48.8	23.1	6.1	6.1
MEAN		9.1	48.2	35.5	3.1	4.2
S.D.		5.2	8.1	8.5	2.7	4.4
2		14.0	36.6	32.6	6.4	10.3
3	72-96	4.8	58.2	36.1	0.7	0.3
4	hours	6.8	55.6	35.6	0.9	1.0
5		4.9	45.7	45.9	1.8	1.7
6		31.6	29.2	29.4	5.1	4.7
MEAN		12.4	45.1	35.9	3.0	3.6
S.D.		11.4	12.3	6.2	2.6	4.1

4. DISCUSSION

As previously discussed (page 26) in the metabolism of paracetamol by the liver a toxic intermediate metabolite is formed which is normally quickly detoxified by hepatic glutathione and subsequently excreted in the urine as the mercapturate and cysteine conjugates. In paracetamol overdosage there is excessive production of this metabolite which results in acute hepatic necrosis when the stores of glutathione are depleted. In this situation there is an increase in the urinary excretion of the mercapturate and cysteine conjugates (Davies et al, 1976; Howie, Adriaenssens and Prescott, 1977).

In chapter 4 it was seen that when patients with decompensated liver disease were given a single dose of paracetamol that the excretion of these two conjugates was not different from those in healthy subjects even though the plasma half-life was significantly prolonged. Although this suggests that such patients have sufficient stores and/or rate of synthesis of glutathione to detoxify the toxic metabolite it gives no insight as to whether they may be able to detoxify the metabolite following repeated doses of paracetamol. If they were not able to do so then further liver damage may result and in this respect it should be noted that toxic hepatitis has been reported in patients said to have taken high therapeutic doses of the drug. (Barker, de Colle and Anuras, 1977; Johnson and Tolman, 1977).

In the present study there was no significant change in the plasma paracetamol half-life measured after the first and last doses of the drug.

In addition,there was no evidence of accumulation of paracetamol in the plasma as there was no significant difference between the plasma concentrations after 24 and 72 hours of drug administration. In none of the patients did the paracetamol administration result in an increase in the plasma ALT concentration, suggesting that the drug had not resulted in any further liver damage. In this context it is of interest that the/

the mean peak plasma paracetamol concentration attained after the last dose of paracetamol (25.0 µg/ml) is considerably less than the plasma concentration which results in acute hepatic necrosis after overdosage (200 µg/ml) (Prescott et al, 1971).

Although there was a slight reduction in the urinary excretion of both the mercapturate and cysteine conjugates in the period 72 - 96 hours compared with the 0-24 hour period these were not significant reductions. However it is worth noting that in 4 of the 5 patients there was a reduction in the mercapturate and in all 5 patients a reduction in the cysteine excretion. This might suggest that hepatic stores of glutathione were becoming depleted and that more prolonged paracetamol administration in such patients could result in liver damage.

5. SUMMARY

6 patients with decompensated liver disease were given 1 gm. of paracetamol 8 hourly for 3 days. There was no significant difference between the plasma paracetamol concentrations at 24 hours (12.4 ± 4.2 µg/ml) and 72 hours (12.2 ± 3.7 µg/ml) and no difference in the plasma half-life measured after the first (5.7 ± 4.2 hours) and the last (5.1 ± 2.5 hours) dose. In none of the patients was there any change in any of the liver function tests. There was a slight but statistically insignificant reduction in the urinary excretion of both the mercapturate and cysteine conjugates in the 72 - 96 hour period compared to the 0 - 24 hour period.

The results show that patients with decompensated liver disease have sufficient stores and/or rate of synthesis of glutathione to detoxify regular therapeutic doses of paracetamol given over a few days and that such administration should not result in further liver damage.

SECTION III

LIGNOCAINE AND ANTIPYRINE METABOLISM IN PATIENTS WITH CHRONIC LIVER DISEASE BEFORE AND AFTER PHENOBARBITONE AND PREDNISOLONE THERAPY AND PORTO-SYSTEMIC SHUNTING

Simultaneous administration of antipyrine and lignocaine

In the previous section it was seen that in patients with chronic liver disease the plasma half-life of lignocaine was prolonged more often and to a greater extent than the antipyrine half-life when compared with the half-lives in healthy subjects. Whilst this may have been due in part to a reduced effective liver blood flow, differences in the relative activity of the two drug metabolising enzyme systems may also have contributed. In an attempt to elucidate further the basis for the relative differences in lignocaine and antipyrine elimination and also to study the effect of various clinical situations on drug metabolism further studies were carried out.

Antipyrine and lignocaine only were studied because of their widely different physico-chemical properties. Their rates of elimination, as judged by the plasma half-life, were studied in three clinical situations:-

1. Before and after phenobarbitone therapy in patients with chronic liver disease
2. Before and after prednisolone therapy in patients with chronic active hepatitis
3. Before and after operation for porto-systemic shunting

In the previous section antipyrine and lignocaine were given separately to patients with chronic liver disease although it would obviously be more convenient if the two test drugs could be given simultaneously. However, as the simultaneous administration of the two drugs could theoretically alter their disposition preliminary studies were first carried out in healthy subjects in which antipyrine and lignocaine were given separately and then together.

CHAPTER 1

STUDIES IN HEALTHY SUBJECTS

1. Study design

Antipyrine and lignocaine were first administered separately to healthy subjects on two different occasions at least 4 days apart and then in combination at least 3 days after the last drug administration.

Antipyrine (18 mg/kg) and lignocaine hydrochloride (Xylotox) (400 mg as powder) were given separately and then together, again dissolved in 50 ml. of dilute orange juice. All 3 studies were performed in the manner previously described (pages 46,47).

For lignocaine, venous blood samples were taken at 0, 2, 4, 6, 8 and 10 hrs. and for antipyrine at 0, 4, 8, 12 and 24 hrs. after administration. The drug half-lives were calculated as before (page 48).

2. Subjects

The studies were carried out on 6 healthy male doctors of mean age 30 years (range 28 - 34 years) and mean weight 68 kg (range 54 - 76 kg). None had a past history of any significant illnesses, particularly jaundice and all were entirely well at the time of the studies. None had been taking any regular medications, and none smoked or abused alcohol.

3. Analytical Methods

Lignocaine in plasma was assayed as previously described (page 44). Antipyrine in plasma was assayed by high performance liquid chromatography (page 40).

4. Results

a. Plasma concentrations

The 2 hour plasma lignocaine and 4 hour plasma antipyrine concentrations when the drugs were given separately and when given in combination are shown in Table XXXVI).

The mean 2 hour lignocaine concentration when the drug was given alone was 0.44 µg/ml (range 0.32 - 0.65 µg/ml) and when given with antipyrine was 0.34 µg/ml (range 0.21 - 0.50 µg/ml). Although 5 of the subjects showed a minor reduction in the plasma concentration of lignocaine when the drug was given with anitpyrine the difference was not significantly different ($t = 2.01$; $p > 0.05$).

The mean 4 hour plasma antipyrine concentration when the drug was given alone was 22.8 µg/ml (range 21.6 - 24.4 µg/ml) and 24.4 µg/ml (range 23.2 - 26.0) when given with lignocaine, all 6 subjects showing and increase in the plasma antipyrine concentration when it was given with lignocaine. Although this was a significant increase ($t = 2.82$; $p < 0.05$), the mean rise was only 7.4% (range 0.9 to 17.8%). There was no correlation between these % changes in theplasma concentrations of the two drugs ($r = 0.22$; $p > 0.01$).

TABLE XXXVI

2 AND 4 HOUR PLASMA CONCENTRATIONS (μg/ml) OF LIGNOCAINE AND ANTIPYRINE IN HEALTHY SUBJECTS FOLLOWING 400 mg LIGNOCAINE HYDROCHLORIDE AND ANTIPYRINE (18 mg/kg) ORALLY WHEN DRUGS GIVEN ALONE AND IN COMBINATION

	2 hr LIGNOCAINE CONCENTRATION			4 hr ANTIPYRINE CONCENTRATION		
SUBJECT NO.	LIGNOCAINE ALONE	LIGNOCAINE WITH ANTIPYRINE	% CHANGE	ANTIPYRINE ALONE	ANTIPYRINE WITH LIGNOCAINE	% CHANGE
1	0.33	0.26	- 21.2	21.9	25.8	+ 17.8
2	0.32	0.28	- 12.5	23.0	23.7	+ 3.0
3	0.65	0.44	- 32.3	23.4	23.6	+ 0.9
4	0.52	0.35	- 32.7	21.6	24.4	+ 13.0
5	0.46	0.21	- 54.3	24.4	26.0	+ 6.6
6	0.40	0.50	+ 25.0	22.5	23.2	+ 3.1
MEAN	0.44*	0.34*	- 21.3	22.8☆	24.4☆	+ 7.4
S.D.	0.12	0.11	26.7	1.0	1.2	6.6

* $p > 0.05$ ☆ $p < 0.05$

b . Plasma half-lives

The plasma half-lives of the two drugs when given separately and together are shown in Table XXXVII.

The mean plasma lignocaine half-life was identical when the drug was given alone and with antipyrine (1.69 hours); 3 of the 6 subjects showing a prolongation and 3 a reduction in the half life.

The mean plasma antipyrine half-life when the drug was given alone was 11.7 hours (range 8.3 - 17.0 hours) and 12.2 hours (range 8.9 - 18.4 hours) when given with lignocaine. Although 5 of the 6 subjects showed an increase in the plasma half-life this was not a significant increase ($t = 2.13$; $p > 0.05$).

There was no correlation between the % changes ($r = 0.33$; $p > 0.1$) in the half-lives of the two drugs when given alone and together.

TABLE XXXVII

PLASMA LIGNOCAINE AND ANTIPYRINE HALF-LIVES (HOURS) IN HEALTHY SUBJECTS WHEN DRUGS GIVEN ALONE AND IN COMBINATION

	Plasma lignocaine half-life			Plasma antipyrine half-life		
Subject No.	Lignocaine alone	Lignocaine with Antipyrine	% change	Antipyrine alone	Antipyrine with Lignocaine	% change
1	2.08	1.95	- 6.3	12.6	13.1	+4.0
2	1.55	1.20	- 22.6	9.0	9.4	+5.0
3	1.68	1.49	- 11.3	8.3	8.9	+7.9
4	1.37	1.45	+ 5.8	10.8	11.2	+4.0
5	1.51	1.97	+ 30.5	12.6	12.3	-2.8
6	1.99	2.13	+ 7.0	17.0	18.4	+8.2
MEAN	1.69*	1.69*	+ 0.5	11.7☆	12.2☆	+4.4
S.D.	0.28	0.36	18.4	3.2	3.4	4.0

*$p > 0.1$

☆$p > 0.05$

5. Discussion

There has apparently been no previous comparison of the plasma half-lives of two drugs given singly and together. In this study the mean 4 hour plasma antipyrine concentration was slightly higher when it was given with lignocaine; no such change being noted with the 2 hour plasma lignocaine concentration. Despite this, the antipyrine and lignocaine half-lives were not significantly different when the drugs were given simultaneously compared with separately. Thus it seemed justifiable to give antipyrine and lignocaine simultaneously to patients with liver disease. It may be conceded, however, that significant differences in the rates of elimination of these two drugs when given together, as opposed to separately, could occur in patients with liver disease but not in healthy subjects.

6. SUMMARY

The plasma concentrations and half-life values of antipyrine and lignocaine were measured in 6 healthy subjects when the drugs were given alone and also when given together.

There was no significant difference in the 2 hour plasma lignocaine concentration when the drug was given alone (mean = 0.44 µg/ml) or with antipyrine (mean = 0.34 µg/ml). The 4 hour plasma antipyrine concentration was significantly higher when the drug was given with lignocaine (mean = 24.4 µg/ml) than when given alone (mean = 22.8 µg/ml); all 6 subjects showing an increase.

The mean plasma lignocaine half-life was the same (1.69 hours) when the drug was given alone or with antipyrine whilst the plasma antipyrine half-life also showed no significant change - mean 11.7 hours when given alone and 12.2 hours when given with lignocaine.

CHAPTER 2

EFFECTS OF PHENOBARBITONE ON THE PLASMA CONCENTRATIONS AND HALF-LIVES OF ANTIPYRINE AND LIGNOCAINE IN PATIENTS WITH CHRONIC LIVER DISEASE

1. PATIENTS

The plasma antipyrine and lignocaine half-lives were measured in 6 patients with chronic liver disease before, and after the administration of phenobarbitone 30 mg. t.i.d. for 5 days. Informed consent was obtained from all patients whose clinical details and diagnoses are given in Table XXXVII. In all cases the diagnosis was established by liver biopsy. Routine liver function tests, P.T.R., serum albumin and plasma urea and electrolytes were measured before each of the studies. If the P.T.R. was initially greater than 1.3 vitamin K_1 (10 mg. intramuscularly) was given on two successive days and the P.T.R. remeasured.

The plasma urea was normal in all patients. There were no significant changes in the patients' clinical status, liver function tests, serum albumin or P.T.R. during the period of the study.

A complete drug history was taken and whenever possible all drugs were stopped before and during the study. 3 patients had been taking drugs regularly for some months: Case 1 methyldopa, bendrofluazide and bethanidine, Case 2 chlorpropamide and frusemide and Case 6 phenylbutazone. In addition cases 2, 4, and 6 started spironolactone 7 - 14 days prior to the study; this continuing during the study. In addition, cases 1, 2, 3 and 4 had been drinking at least 80 gm. of alcohol per day and case number 6 less than 40 gm. per day until 14 - 21 days prior to the study when all alcohol consumption stopped.

At the time of the study the clinical state of all patients was stable and none was in cardiac failure. All were hospital in-patients for the duration of the study.

TABLE XXXVIII

CLINICAL AND LABORATORY DETAILS

Patient No.	Age (yrs)	Sex	Weight (kg)	Diagnosis	Bilirubin (µmol/l)	ALT (units/l)	Alkaline phosphatase (units/l)	Albumin (gm/l)	Prothrombin Time Ratio
1	61	F	65	Alcoholic cirrhosis	169	41	167	38	1 · 3
2	54	M	70	Alcoholic hepatitis	47	33	212	34	1 · 3
3	49	M	87	Alcoholic cirrhosis	49	28	188	33	1 · 3
4	27	M	53	Alcoholic cirrhosis	70	29	280	32	1 · 3
5	66	M	74	Alcoholic cirrhosis	45	47	142	27	1 · 3
6	58	M	70	Alcoholic cirrhosis	48	30	74	26	1 · 5

2. DESIGN OF STUDY

After an overnight fast antipyrine (18 mg/kg) and lignocaine hydrochloride ('Xylotox') (400 mg.) were given together; the study being performed as previously described (pages 46,47). Venous samples were withdrawn at 0, 2, 4, 6, 8, 12 and 24 hours for estimation of plasma lignocaine and at 0, 4, 8, 12, 24 and 36 hours for plasma antipyrine.

On completion of the first study the patients were given phenobarbitone 30 mg. 8 hrly for 5 days. On the 6th day antipyrine and lignocaine were again administered and blood samples taken for drug assay as before. At the time of the antipyrine and lignocaine administration venous blood was taken for estimation of the plasma phenobarbitone concentration.

3. ANALYTICAL METHODS

a. Plasma antipyrine and lignocaine were estimated by high performance liquid chromatography as previously described (pages 40,44).

b. Phenobarbitone in plasma was estimated by gas-liquid chromatography (Prescott unpublished).

To 1 ml. of plasma was added 1 ml. of water containing 10 µg cyproheptadine internal standard and 1 ml. 1M phosphate buffer pH 6.8. The drugs were extracted into 5 ml. diethyl ether. After centrifuging the mixture was frozen., the upper organic layer decanted into conical tubes and the ether dried off in a water bath at 45°C with a draught of air blown over the tops of the tubes. The residue was re-constituted with 30 µl of ethanol.

A Hewlet-Packard Model 402 gas chromatograph fitted with a nitrogen-sensitive flame ionisation detector was used with a 3ft x $\frac{1}{4}$" o.d. glass column packed with 2% OV 17 + 1% OV 225 on 100 mesh Chromosorb G80 maintained at 212°C. The concentrations of phenobarbitone were/

were calculated from the peak height ratios of phenobarbitone to internal standard using standards run throughout the procedure at the same time as the unknown samples.

The S.D. of the assay was 4.4% over the range 5 - 50 µg/ml.

3. RESULTS

a. PLASMA PHENOBARBITONE CONCENTRATIONS

The plasma phenobarbitone concentrations in the patients in relation to the time of the last dose of phenobarbitone are shown in Table XXXIX. The plasma concentrations ranged from 4.4 µg/ml to 8.8 µg/ml (mean 7.0 µg/ml).

TABLE XXXIX

PLASMA PHENOBARBITONE CONCENTRATIONS (µg/ml) IN PATIENTS WITH CHRONIC LIVER DISEASE AFTER PHENOBARBITONE 30 mg. t.i.d. FOR 5 DAYS.

PATIENT NO.	PHENOBARBITONE CONCENTRATION (µg/ml)	TIME AFTER LAST DOSE (HOURS)
1	8.1	3
2	7.5	3
3	7.3	11
4	5.6	15
5	8.8	11
6	4.4	11

b. PLASMA ANTIPYRINE AND LIGNOCAINE CONCENTRATIONS

The initial plasma concentrations of lignocaine (2 hours after ingestion) and antipyrine (4 hours after ingestion) are shown in Table XXXX.

The mean 2 hour lignocaine concentration was 1.58 µg/ml (range 0.46 - 2.95 µg/ml) before treatment with phenobarbitone falling to a mean value of 1.14 µg/ml (range 0.36 - 2.68) after treatment; all 6 patients showing a decrease. This was a statistically significant fall ($t = 2.60$ $p < 0.05$). The mean percentage decrease was 29% (range 9 - 48%).

The changes in the plasma antipyrine concentrations following phenobarbitone were much less; the mean concentration being 30.9 µg/ml (range 24.4 - 37.0 µg/ml) before treatment and 28.2 µg/ml (range 21.6 - 36.3 µg/ml) after treatment. This was not a statistically significant decrease ($t = 2.16$; $p > 0.05$); only 4 of the patients showing a fall with treatment. The mean percentage decrease was 9% (range -22.4 to +2.0%).

There were no statistically significant correlations between the serum albumin and P.T.R., the pre-treatment plasma lignocaine and antipyrine half-lives and the pre-treatment 2 hr plasma lignocaine and 4 hr antipyrine concentrations and the % change in these concentrations following phenobarbitone ($r = 0.39$, $p > 0.1$).

TABLE XXXX

2 HOUR PLASMA LIGNOCAINE AND 4 HOUR PLASMA ANTIPYRINE CONCENTRATIONS IN PATIENTS WITH CHRONIC LIVER DISEASE FOLLOWING 400 mg LIGNOCAINE HYDROCHLORIDE AND ANTIPYRINE (18mg/kg) ORALLY BEFORE AND AFTER 5 DAYS TREATMENT WITH PHENOBARBITONE (90 mg DAILY)

	2 HOUR LIGNOCAINE CONCENTRATION			4 HOUR ANTIPYRINE CONCENTRATION		
PATIENT NO.	BEFORE PHENOBARBITONE	AFTER PHENOBARBITONE	% CHANGE	BEFORE PHENOBARBITONE	AFTER PHENOBARBITONE	% CHANGE
1	2.43	1.30	-45.8	36.0	36.3	+0.8
2	1.12	0.66	-41.1	37.0	31.6	-14.6
3	0.46	0.36	-21.7	32.1	29.8	- 7.2
4	1.11	0.58	-47.7	30.4	23.7	-22.4
5	1.45	1.30	-10.3	25.4	25.9	+ 2.0
6	2.95	2.68	- 9.2	24.4	21.6	-11.5
MEAN	1.58*	1.14*	-29.3	30.9☆	28.2☆	- 8.8
S.D.	0.92	0.84	17.7	5.24	5.45	9.4

* $p < 0.05$

☆ $p > 0.05$

c . PLASMA ANTIPYRINE AND LIGNOCAINE HALF-LIVES

The plasma half-lives of anitpyrine and lignocaine before and after phenobarbitone are shown in Table XXXXI and Fig.14.
With regard to antipyrine the mean plasma half-life was 36.4 hours (range 17.6 - 61.2 hours) before phenobarbitone falling to 28.9 hours (range 9.1 - 55.4 hours) after treatment. The mean percentage reduction was 20.3% (range -49 to +6.0%); 5 of the 6 patients having a shortening in the half-life. However, this was not a statistically significant reduction ($t = 1.55$; $p > 0.1$).

The lignocaine half-life, also, showed no significant change with treatment ($t = 0.35$; $p > 0.70$); the mean plasma half-life being 5.6 hours (range 2.8 - 8.4 hours) before phenobarbitone and 5.5 hours (range 2.3 - 9.7 hours) after therapy. The mean percentage change was 5.7% (range -35 to +24%); 5 of the 6 patients showing a decrease in the plasma half-life after therapy.

Only 1 patient (no. 4) showed a substantial shortening of both the antipyrine and lignocaine half-lives; antipyrine (-49.2%) and lignocaine (-35%).

There were no statistically significant correlations between the serum albumin and P.T.R., the 2 hr lignocaine and 4 hr antipyrine plasma concentrations and the plasma half-lives of the two drugs before phenobarbitone and the percentage change in either drug half-life with phenobarbitone ($r \leq 0.50$; $p > 0.05$). In addition there was no correlation between the percentage change in the two drug half-lives following phenobarbitone ($r = 0.65$; $p > 0.05$).

TABLE XXXXI

PLASMA ANTIPYRINE AND LIGNOCAINE HALF-LIVES (HOURS) IN PATIENTS WITH CHRONIC LIVER DISEASE BEFORE AND AFTER 5 DAYS TREATMENT WITH PHENOBARBITONE 90 mg. DAILY.

	ANTIPYRINE HALF-LIFE			LIGNOCAINE HALF-LIFE		
PATIENT NO.	BEFORE PHENOBARBITONE	AFTER PHENOBARBITONE	% CHANGE	BEFORE PHENOBARBITONE	AFTER PHENOBARBITONE	% CHANGE
1	56.5	55.4	- 1.9	7.8	9.7	+24.4
2	22.8	19.4	-14.9	5.6	5.0	-10.3
3	28.6	24.8	-13.3	2.75	2.7	- 1.1
4	17.6	9.1	-48.3	3.6	2.3	-35.0
5	61.2	31.1	-49.2	8.4	7.8	- 7.2
6	31.7	33.6	+ 6.0	5.6	5.3	- 4.8
MEAN	36.4*	28.9*	-20.3	5.6☆	5.46☆	- 5.7
S.D.	18.1	15.7	24.4	2.2	2.9	19.0

*$p > 0.1$

☆$p > 0.7$

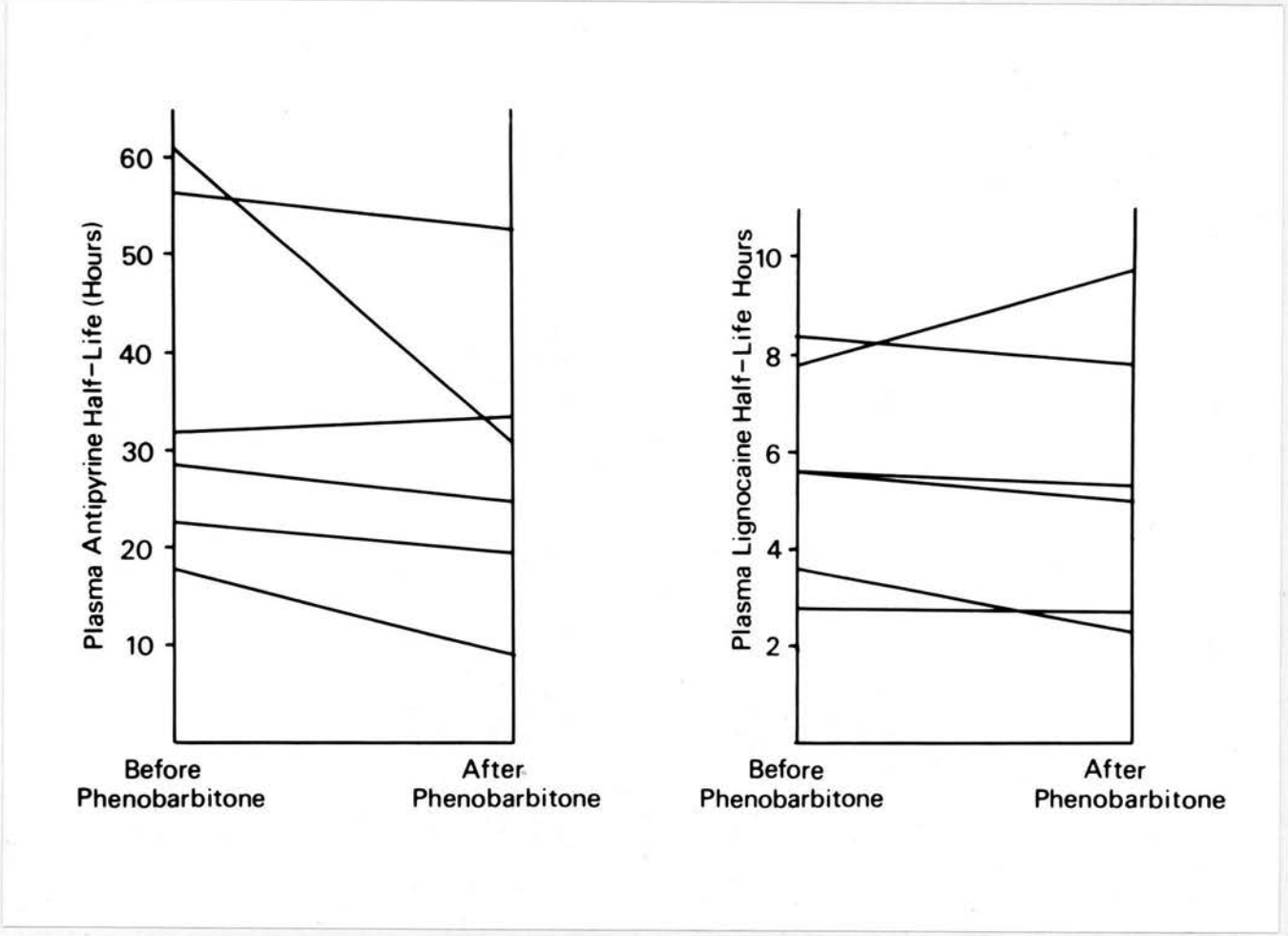

Fig. 14

Plasma antipyrine half-life in 6 patients with chronic liver disease before and after treatment with phenobarbitone (30 mg. t.i.d. for 5 days).

4 DISCUSSION

Many studies on healthy subjects have shown phenobarbitone to be a potent inducer of hepatic microsomal enzymes. MacDonald et al., (1969), and Breckenridge et al.(1973) noted a significant reduction in both plasma warfarin concentrations and half-lives following 21 - 30 days treatment with phenobarbitone, whilst Kampffmeyer (1971) reported a reduction in the half-life of antipyrine of 40%. Microsomal induction begins at about one week (Robinson & MacDonald, 1966; Breckenridge et al., 1973) and reaches a maximum by 20 - 26 days (Breckenridge et al., 1973). However, Corn (1966) has shown that induction can occur as soon as 48 hours after starting phenobarbitone.

Phenobarbitone causes a non-specific increase in hepatic microsomal enzyme activity which is the result of an increase in the amount of enzyme rather than a change in theproperties of the enzymes (Conney et al., 1960). It accelerates many biotransformations (Parke, 1971) and not all are equally affected. The inducing effect is not limited to the microsomal enzymes with an increase in mitochondrial (δ -amino-laevulinic acid synthetase) and cytoplasmic enzymes (aldehyde dehydrogenase). In addition there is an increase in the rate of synthesis of certain proteins e.g. X and Y proteins.

There is however, little information of the inducing effect of phenobarbitone - or indeed other drugs - in patients with chronic liver disease. Although Branch, Herbert & Read (1973) noted that 3 days of treatment with 90 mg of phenobarbitone daily produced a 30% shortening in the plasma antipyrine half-life in a heterogenous group of patients with liver disease, the effect of phenobarbitone on the elimination of different drugs has not been studied in patients with chronic liver disease.

In the present study phenobarbitone given for 5 days had an unpredictable and varying effect on both the plasma antipyrine and lignocaine half-lives. However, the plasma concentrations of phenobarbitone following 5 days treatment were all below the normal therapeutic range of 10 - 30 µg/ml (Woodbury & Fingl, 1975b) , and a different result might have been obtained if larger doses had been given for a longer period.

There was a moderate (20%), though statistically insignificant, reduction in the mean antipyrine half-life following phenobarbitone and only a minor (6%) reduction in the mean lignocaine half-life. Although phenobarbitone exerts its main effect on the microsomal enzyme activity it may also produce changes in liver blood flow. Thus although barbiturate treatment has been found to increase hepatic blood flow in animals (Ohnhaus et al., 1971), no such increase has been found in patients without liver disease following treatment with phenobarbitone (Roberts et al., 1976) and pentobarbitone (Alván et al., 1977). There is no information on the effects of phenobarbitone on liver blood flow in patients with liver disease. The results of this study are consistent with the pharmacokinetic properties of the two drugs studied. The rate of lignocaine elimination depends largely on liver blood flow rather than the hepatic enzyme activity and phenobarbitone with its predominant effect on the microsomal enzymes would not be expected to influence its half-life to any extent. On the other hand, the rate of elimination of antipyrine which has a low hepatic extraction ratio depends on enzyme activity rather than liver blood flow and hence a reduction in the plasma half-life would be expected after phenobarbitone treatment.

In this study enzyme reduction could also be partly due to an increase in protein consumption (Kappas et al., 1977) and / or correction of vitamin C deficiency (Beattie & Sherlock, 1976).

With neither drug could the changes in half-life be related to any of the clinical parameters or to the drug half-life prior to starting phenobarbitone. This is in keeping with the findings in healthy subjects of Breckenridge et al., (1973) who noted that (using quinalbarbitone) there was no correlation between the fall in the steady state warfarin concentrations or half-life and the pre-treatment rate of warfarin metabolism. In addition, in studies on healthy twins given phenobarbitone **Vesell** and Page (1969) failed to show a correlation between the plasma concentrations of phenobarbitone and the shortening of the plasma antipyrine half-life although a correlation was noted between the degree of shortening of the half-life and the pre-induction plasma antipyrine half-life. The effects between twins varied suggesting that different subjects required different plasma concentrations of phenobarbitone to produce the same effect. As previously mentioned, there is little information on the inducing effect of barbiturates in patients with liver disease. Animal studies (Kato et al., 1964) suggest that barbiturates have less inducing effect in the elderly and there may be a similar effect in liver disease.

Phenobarbitone therapy significantly reduced the 2 hour plasma lignocaine concentration but had no such effect on the 4 hour plasma antipyrine concentration. This finding is to be expected since the extensive first pass metabolism of lignocaine with its high hepatic extraction ratio would be increased still further by phenobarbitone whilst there would be no change in antipyrine with its low extraction ratio. Similar findings have been reported by Alván, et al., (1977) who showed that pentobarbitone increased the hepatic extraction of alprenolol - a drug with a high hepatic extraction ratio - by 30% with no attendant increase in liver blood flow.

5. SUMMARY

Phenobarbitone (30 mg. t.i.d.) was given for 5 days to 6 patients with chronic liver disease; the plasma antipyrine and lignocaine concentrations and half-lives being measured before and after treatment There was a moderate (20%) , but statistically insignificant reduction in the mean plasma antipyrine half-life following phenobarbitone (from 36.4 hours to 28.9 hours) and a minor reduction (6%) in the mean plasma lignocaine half-life (from 5.6 hours to 5.5 hours). In neither drug could changes in the plasma half-life with phenobarbitone be related to any of the clinical parameters or to the drug half-life prior to starting phenobarbitone.

There was a significant reduction (29%) in the mean 2 hour plasma lignocaine concentration following phenobarbitone (from 1.58 µg/ml to 1.14 µg/ml) but only a minor (9%) reduction in the 4 hour plasma antipyrine concentration following therapy (from 30.9 µg/ml to 28.2 µg/ml).

CHAPTER 3

EFFECT OF PREDNISOLONE ON THE PLASMA HALF-LIVES OF ANTIPYRINE AND LIGNOCAINE IN PATIENTS WITH CHRONIC ACTIVE HEPATITIS

1. Patients

Studies were performed in 3 patients with chronic active hepatitis as established by liver biopsy. The plasma antipyrine and lignocaine half-lives were measured in two patients before treatment with prednisolone was commenced and subsequently when the routine liver function tests, plasma albumin and P.T.R. had returned to normal (case no. 2) or had improved considerably (case no. 3). In the other case (case no. 1) the patient was on long term prednisolone. In this patient the plasma half-lives of the two drugs were first studied during an exacerbation of the hepatitis and then after a period of increased prednisolone therapy which improved the routine liver function tests.

The clinical and laboratory details of the patients studied are shown in Table XXXXII. Routine liver function tests, P.T.R., serum albumin and plasma urea and electrolytes were measured before each of the two studies. If the P.T.R. was initially greater than 1.3, vitamin K_1 (10mg intramuscularly) was given on two successive days and the P.T.R. remeasured; this P.T.R. being used. The plasma urea and electrolytes were normal in all 3 patients at the time of both studies. None of the 3 patients took alcohol and only case no. 3 smoked cigarettes (10/day), At the time of the two studies none of the patients was in cardiac failure or had ascites.

Case no. 1 had been on prednisolone intermittently for 4 years and prior to the first study had been taking 10mg/day for some months. The drug half-lives were first estimated during an exacerbation in her hepatitis - as evidenced by a rise in her serum bilirubin, ALT and alkaline phosphatase and a fall in her plasma albumin. They were again/

again measured following 16 days treatment with prednisolone in an increased dose of 30mgs per day. Prior to the first study the patient had been taking bendrofluazide and warfarin; both drugs being continued between the two tests.

Case no. 2 The plasma drug half-lives were measured before commencing prednisolone (30mgs per day) and then 146 days later whilst still taking 17.5 mgs/day. The patient had been on no therapy prior to the first study and on bendrofluazide in addition to prednisolone between the two studies.

Case no. 3 The plasma drug half-lives were measured before commencing prednisolone (30mgs/day) and then 152 days later whilst still taking 10 mgs/day. The patient had been on no therapy prior to the first study and on no other therapy apart from prednisolone between the two studies.

2. Design of study

Both studies were carried out in an identical manner. After an overnight fast antipyrine (18mg/kg) and lignocaine hydrochloride (xylotox) (400mg) were given together; the study being performed as previously described (pages 46,47). Venous samples were withdrawn at 0, 2, 4, 6, 8, 12 and 24 hours for estimation of plasma lignocaine and at 0, 4, 8, 12, 24 and 36 hours for plasma antipyrine.

Case no. 1 was in hospital for both studies, whilst cases 2 and 3 were out-patients when the second study was performed.

TABLE XXXXII

CLINICAL AND LABORATORY DETAILS

			BEFORE PREDNISOLONE					AFTER PREDNISOLONE				
Patient	Age:Sex	Wt (kg)	Bilirubin (µmol/l)	ALT (units/l)	Alkaline phos-phatase (units/l)	Albumin (gm/l)	PTR	Bilirubin	ALT	Alkaline phos-phatase	Albumin	PTR
1	65:F	49*	149	150	25	33	1.3	60	36	244	35	1.3
2	66:F	67	156	236	251	28	1.2	14	23	135	43	1.2
3	55:F	70	296	540	335	29	1.6	11	73	139	43	1.3

* Already taking prednisolone (10 mg / day) prior to initial study

3. Results

a. Plasma concentrations

The 2 hour lignocaine and 4 hour plasma antipyrine concentrations before and after prednisolone therapy are shown in Table XXXXIII. With regard to lignocaine all 3 patients showed a reduction in the plasma concentration after prednisolone therapy, from a mean value of 0.71 µg/ml to 0.57 µg/ml (16.5%). The changes in the 4 hour plasma antipyrine concentrations were much less, only 2 of the patients showing a fall with prednisolone; the mean concentration falling with treatment from 31.7 µg/ml to 28.4 µg/ml (9.7%). In neither case were these changes significant ($t = 1.42$ and 1.29; $p > 0.3$).

TABLE XXXXIII

2 HOUR PLASMA LIGNOCAINE AND 4 HOUR PLASMA ANTIPYRINE CONCENTRATIONS FOLLOWING LIGNOCAINE HYDROCHLORIDE (400 mg) AND ANTIPYRINE (18mg/kg) IN PATIENTS WITH CHRONIC ACTIVE HEPATITIS BEFORE AND AFTER TREATMENT WITH PREDNISOLONE

	2 HOUR LIGNOCAINE CONCENTRATION			4 HOUR ANTIPYRINE CONCENTRATION		
CASE NO.	BEFORE PREDNISOLONE	AFTER PREDNISOLONE	% CHANGE	BEFORE PREDNISOLONE	AFTER PREDNISOLONE	% CHANGE
1	0.57	0.48	-15.8	28.2	29.4	+ 4.3
2	0.59	0.58	- 1.7	33.4	26.1	-21.9
3	0.97	0.66	-32.0	33.5	29.6	-11.6
MEAN	0.71	0.57	-16.5	31.7	28.4	- 9.7

b. Plasma half-lives

The plasma lignocaine and antipyrine half-live before and after prednisolone are shown in Table XXXXIV.

All 3 patients showed a substantial reduction in both the drug half-lives. The mean lignocaine half-life fell from 6.07 to 3.48 hours with prednisolone (42%); whilst the changes in the antipyrine half-life were more marked. The mean half-life fell from 49.9 to 19.3 hours (56%); two of the 3 patients having reductions of 70 and 74% (from 46.8 and 68.8 hours to 13.9 and 17.9 hours respectively). In neither case, however, were these changes statistically significant. ($t = 2.84$ and 2.46; $p > 0.2$)

TABLE XXXXIV

PLASMA LIGNOCAINE AND ANTIPYRINE HALF-LIVES (HOURS) IN PATIENTS WITH CHRONIC ACTIVE HEPATITIS BEFORE AND AFTER TREATMENT WITH PREDNISOLONE

	LIGNOCAINE HALF-LIFE			ANTIPYRINE HALF-LIFE		
CASE NO.	BEFORE PREDNISOLONE	AFTER PREDNISOLONE	% CHANGE	BEFORE PREDNISOLONE	AFTER PREDNISOLONE	% CHANGE
1	6.11	3.41	-44.2	34.2	26.2	-23.4
2	6.58	3.53	-46.2	46.8	13.9	-70.3
3	5.52	3.51	-36.4	68.8	17.9	-74.0
Mean	6.07	3.48	-42.3	49.9	19.3	-55.9

4. DISCUSSION

In chronic active hepatitis treatment with prednisolone usually results in a reduction in the degree of hepatic necrosis and an increase in the number of functioning hepatocytes with a consequent return of the liver function tests and plasma albumin to normal.

Thus following prednisolone therapy any improvement in the rate of drug metabolism could either result from an increase in the number of functioning hepatocytes and/or from an increase in the activity of the enzymes, as the drug is a known inducing agent (Conney, 1967).

There have been few studies of drug metabolism in patients with chronic active hepatitis treated with prednisolone. Thus, although Branch, James and Read (1973) noted that the plasma antipyrine half-life was significantly longer in a group of patients with untreated chronic active hepatitis than another group who had been treated with prednisolone there have apparently been no studies of drug metabolism in the same patients before and after prednisolone therapy.

In this study all 3 patients showed a reduction in both the plasma antipyrine and lignocaine half-lives following treatment with prednisolone. The mean reduction in the lignocaine half-life (42%) was less than the antipyrine half-life (56%). Indeed in cases 2 and 3 where the drug half-life was measured after some months of treatment with prednisolone, when the serum albumin and P.T.R. had returned to normal, the reduction in the antipyrine half-life was 70 and 74% respectively - to values in the range seen in healthy subjects. Although these changes for both drugs were not statistically significant - perhaps because of the small numbers - they nevertheless represent major changes.

These changes are, in part, what might be predicted from the hepatic extraction ratios of the drugs. The rate of metabolism of antipyrine is dependent both on the number of functioning hepatocytes and their degree of enzyme activity; both of which would be increased by prednisolone. Thus after prednisolone there /

there was a large reduction in the antipyrine half-life. On the other hand the rate of metabolism of lignocaine is much more dependent on liver blood flow. Hence it is perhaps a little surprising that there has been such a large reduction in the lignocaine half-life with prednisolone. It is conceivable however that, in addition to or consequent of its other effects, prednisolone reduces intra-hepatic shunting and thus increases liver blood flow to the hepatocytes.

The changes in the 2 hour plasma lignocaine and 4 hour antipyrine concentrations following prednisolone were quite small, antipyrine (9.7%) being less than lignocaine (16.5%). These findings are in keeping with the hepatic extraction ratios of the drugs. Thus the small reduction in the 2 hour lignocaine concentration after prednisolone could be due to an increase in effective liver blood flow and hence a reduction in "first-pass" losses. As antipyrine metabolism is not dependent on liver blood flow one would expect no change in the initial plasma concentration after prednisolone; this occurred in this study.

5. SUMMARY

The metabolism of lignocaine and antipyrine was studied in 3 patients with chronic active hepatitis before, and a mean of 105 days after commencing treatment with prednisolone. In two of the 3 cases routine liver function tests had returned to normal before the repeat study was carried out. Following prednisolone therapy the mean lignocaine half-life shortened from 6.07 to 3.48 hours (42%) and the mean antipyrine half-life from 49.9 to 19.3 hours (56%). In two cases the reduction in the antipyrine half-life was 70 and 74%.

Prednisolone produced little change in the 2 hour plasma lignocaine and 4 hour plasma antipyrine concentrations; the former changing from a pre-treatment mean of 0.71 µg/ml to 0.57 µg/ml (16.5%) after therapy and the latter from 31.7 to 28.4 µg/ml (10%).

CHAPTER 4.

EFFECT OF PORTO-SYSTEMIC SHUNTING ON ANTIPYRINE AND LIGNOCAINE METABOLISM IN PATIENTS WITH CIRRHOSIS AND PORTAL HYPERTENSION.

The rate of antipyrine and lignocaine elimination from the plasma was measured in 4 patients with portal hypertension before and after a lieno-renal shunt operation had been performed. This was carried out to reduce portal venous pressure because of recurrent bleeding from oesophagael varices.

1. Patients

The clinical and laboratory details of the patients studied are shown in TableXXXXV. Prior to the operation all had relatively good liver function. In patient no. 3 the low albumin and prolonged P.T.R. pre-operatively may have been secondary to an acute episode of bleeding. At the time of both studies none of the patients were in cardiac failure and only one (patient no. 2) had a slightly raised plasma urea (8.2mmol /l) at the time of the second study only. Patients 1 and 2 were on no drugs prior to the first study but had been taking spironolactone prior to the second study. Patient no. 3 had been on spirocolactone and frusemide and patient 4 (a diabetic) on spironolactone, frusemide and chlorpropamide prior to both studies. None of the patients smoked or took alcohol.

The pre-operative assessment of the rate of antipyrine and lignocaine elimination was carried out 1 - 9 days before the operation in patients 1, 2 and 4 and 150 days in patient no. 3. The repeat study was carried out 13 - 213 days (mean 111) after the operation.

2. Design of Study/

TABLE XXXXV

CLINICAL AND LABORATORY DETAILS

Patient no.	Age:Sex	wt (kg)	Diagnosis	PRE-SHUNT serum albumin (gm/l)	PRE-SHUNT P.T.R.	POST-SHUNT serum albumin (gm/l)	POST-SHUNT P.T.R.	Interval between shunt and repeat test (days)
1	57:F	26	cryptogenic cirrhosis	36	1.3	29	1.3	13
2	60:F	61	cryptogenic cirrhosis	39	1.3	35	-	83
3	49:M	79	α_1-anti-tripsin deficiency and cirrhosis	28	1.5	40	1.3	213
4	70:M	55	cryptogenic cirrhosis	32	1.3	33	1.3	107

2. Design of Study

This was carried out as previously described (pages 46,47) antipyrine (18 mg/kg) and lignocaine hydrochloride ('xylotox') (400mg) being given orally on both occasions.

3. Analytical Methods

Antipyrine was estimated by high performance liquid chromatography (page 40) and lignocaine by gas-liquid chromatography (page 44).

4. Results

a. Plasma drug concentrations

The 2 hour plasma lignocaine and 4 hour plasma antipyrine concentrations before and after the lieno-renal shunt operation are shown in Table XXXXVI.

With regard to lignocaine two patients showed an increase in the 2 hour plasma concentrations after the operation and two a decrease. Only one patient (no. 1) showed a marked increase and the mean change following operation was only +2%.

After the shunt the 4 hour plasma antipyrine concentration was slightly reduced in 3 patients; the overall mean change being -10%.

For neither drug were the changes in the plasma concentrations significant ($t = 0.33$ and $2.04 : p \geq 0.1$).

TABLE XXXXVI

2 HOUR PLASMA LIGNOCAINE AND 4 HOUR PLASMA ANTIPYRINE CONCENTRATIONS (μg/ml) IN PATIENTS BEFORE AND AFTER PORTO-SYSTEMIC SHUNTING FOLLOWING LIGNOCAINE HYDROCHLORIDE (400 mg) AND ANTIPYRINE (18 mg/kg) ORALLY.

	2 hour lignocaine concentration		4 hour antipyrine concentration	
Patient no.	pre-shunt	post-shunt	pre-shunt	post-shunt
1	2.46	4.39	22.2	17.0
2	0.60	0.40	32.2	29.5
3	2.34	1.23	30.3	27.1
4	2.66	2.89	28.0	28.4
Mean	2.02	2.23	28.2	25.5

b. Plasma drug half-lives

The lignocaine and antipyrine plasma half-lives before and after the operation are shown in Table XXXXVII.

Following the operation there was a prolongation in the lignocaine half-life in 3 patients; one (patient no. 4) showing a marked prolongation from 2.83 to 6.12 hours (116%). The mean change was from 3.47 to 4.30 hours (+40%).

Following the shunt the antipyrine half-life was prolonged in 3 patients; one (patient no. 2) showing a marked prolongation from 10.5 to 23.0 hours (119%).

In one patient (no. 3) the operation resulted in a marked decrease in both the lignocaine (from 5.52 to 2.74 hours) and antipyrine (from 42.9 to 29.7 hours) half-lives.

In the patients overall the changes in the plasma half-lives of both drugs were not significant ($t = 0.63$ and 0.85; $p > 0.1$), and there was no correlation between the percentage change in each drug half-life. ($r = 0.34$; $p > 0.1$)

c. Plasma clearance of antipyrine

The plasma clearances of antipyrine before and after the operation are shown in Table XXXXVII. Following the shunt 3 patients showed a decreased and 1 (patient no. 3) an increased clearance.

The mean clearance was 19.1 mls/min pre-operatively and 15.5mls/min post-operatively (a 16% change). This was not significant ($t = 1.08$; $p > 0.1$).

d. Volume of distribution of antipyrine

The volumes of distribution of antipyrine before and after the operation are shown in Table XXXXVII. Following the operation the volume of distribution increased in 3 patients and decreased in 1 (patient no. 3). The mean volume of distribution pre-operatively was 33.21 and post-operatively 33.91. This was not a significant change ($t = 0.23$; $p > 0.1$).

TABLE XXXXVII

PLASMA HALF-LIFE, PLASMA CLEARANCE AND VOLUME OF DISTRIBUTION (V_D) OF ANTIPYRINE AND PLASMA HALF-LIFE OF LIGNOCAINE BEFORE AND AFTER PORTO-SYSTEMIC SHUNTING.

	ANTIPYRINE						LIGNOCAINE	
	Plasma $T\frac{1}{2}$(hours)		Plasma clearance (mls/min)		V_D (l)		Plasma $T\frac{1}{2}$(hours)	
Patient no.	pre-shunt	post-shunt	pre-shunt	post-shunt	pre-shunt	post-shunt	pre-shunt	post-shunt
1	9.4	13.7	19.3	18.8	15.7	19.9	2.00	2.56
2	10.5	23.0	28.8	16.6	26.2	33.0	3.53	5.78
3	42.9	29.7	15.2	18.5	56.6	47.6	5.52	2.74
4	30.2	51.4	13.0	7.9	33.9	35.1	2.83	6.12
Mean	23.3	29.5	19.1	15.5	33.2	33.9	3.47	4.30

5. Discussion

Although liver function is known to deteriorate after porto-systemic shunting there have, apparently, been no previous studies of drug metabolism before and after such an operation. Branch, James and Read (1976a) did, however, find that in two groups of patients with a similar severity of chronic liver disease those who had undergone a porto-systemic shunt had a significantly longer plasma half-life and a significantly lower plasma clearance of antipyrine and indocyanine green than those in whom no such operation had been carried out.

In this present study the serum albumin fell in 3 patients after the operation; although there was no consistent change in the P.T.R. In conjunction with the albumin changes these patients also showed an increase in the plasma antipyrine and lignocaine half-lives and a decrease in the antipyrine clearance after the operation. In two patients the changes in the plasma half-lives and clearance were moderate but in one patient the antipyrine and lignocaine half-lives were prolonged by 119% and 64% respectively. This reduction in the plasma half-life of antipyrine was mainly secondary to a reduced plasma clearance of the drug ; the increase in the volume of distribution being minimal. In one patient the serum albumin rose after the procedure. This may possibly be explained by the fact that the pre-shunt albumin estimation was carried out just after a major gastro-intestinal bleed which may have impaired his liver function. This rise in albumin post-operatively was accompanied by a decrease in the plasma antipyrine and lignocaine half-lives and an increase in the plasma antipyrine clearance.

It is of interest that following the operation, the mean percentage increase in the lignocaine half-life (40%) was greater than that of antipyrine (21%). This is in keeping with the findings of Branch, James and Read (1976a) who found that patients with a porto-systemic shunt/

shunt had a longer prolongation of the indocyanine green half-life than the antipyrine half-life when compared with these half-lives in patients with chronic disease of similar severity but without a shunt. These findings might be expected on the basis of the hepatic extraction ratios of the drugs. Thus if following the shunt there was a reduction in the effective liver blood flow, this would tend to have a greater effect on lignocaine, with its high hepatic extraction ratio, than antipyrine with its low extraction ratio. In this situation it might be expected that following the shunt there would be a decrease in first pass metabolism and hence an increase in the 2 hour plasma lignocaine concentration. This, however, was not the case; only one patient showing a marked rise. Indeed the mean rise in the 2 hour plasma lignocaine concentration was only slightly greater than that of the 4 hour plasma antipyrine concentration. This might suggest that the shunt had produced a differential effect on the two drug metabolising enzyme systems.

6. Summary

The metabolism of lignocaine and antipyrine was measured in 4 patients with cirrhosis and portal hypertension before, and a mean of 111 days after a lieno-renal shunt had been carried out.

Following the operation there was a prolongation in the lignocaine half-life from 3.47 to 4.30 hours and in the antipyrine half-life from 23.3 to 29.5 hours. The antipyrine clearance fell from 19.1 to 15.5mls/min following the operation. None of these changes were significant. There were also no significant changes in the 2 hour plasma lignocaine and 4 hour plasma antipyrine concentrations following the operation.

SECTION IV

ANTIPYRINE METABOLISM IN PARACETAMOL-INDUCED ACUTE HEPATIC NECROSIS

ANTIPYRINE METABOLISM IN ACUTE HEPATIC NECROSIS

1. PATIENTS AND DESIGN OF STUDY

The ability of patients with acute hepatic necrosis secondary to paracetamol overdosage to eliminate antipyrine was studied in 17 patients. These patients were admitted to the Regional Poisoning Treatment Centre, Royal Infirmary, Edinburgh, following acute paracetamol overdosage; the antipyrine half-life being assessed on two occasions. Firstly, as soon as the patient was clinically well enough following the acute overdosage (n = 17) and secondly 7 - 63 days later when they had made a full clinical recovery (n = 8).

The clinical and laboratory details are shown in Table XXXXVIII. Apart from one patient (case 9) who was a chronic alcoholic,none was known to have pre-existing liver disease. Four patients had been taking drugs regularly prior to the overdosage. Case 4 had been taking phenobarbitone and cases 2, 12 and 15 fluphenazine with orphenadrine, Minovlar (norethisterone) and nitrazepam respectively. Two patients had taken alcohol at the time of the overdosage, (nos. 9 and 13). No treatment was required apart from 2 patients (cases 2 and 12) who required fresh frozen plasma.

The severity of the hepatic necrosis was assessed by daily measurement of the P.T.R., serum alanine aminotransferase (ALT) activity and bilirubin concentration.

Plasma paracetamol concentrations were determined on admission in 15 cases, and in 14 cases blood samples were taken at regular intervals for up to 36 hours for estimation of the plasma paracetamol half-life.

In patients with mild to moderate liver damage the antipyrine half-life was usually assessed within 2 days of admission but in those with severe hepatic necrosis the administration of antipyrine was delayed until there was clinical and/or biochemical evidence of recovery. The mean interval between admission and the initial antipyrine study/

study was 3.2 days (range 1.5 - 7 days) (Table XXXXIX). In 9 of the 17 patients (53%) this initial study was carried out within 48 hours of admission.

The antipyrine half-life was determined again in 8 of these patients. In 5 patients (case nos. 8, 12, 13, 14 and 15) the second study was carried out 7 days after the first and in the remaining three the intervals were 21 days (cases 2 and 16) and 63 days (case 9). At this time routine liver function tests were again measured.

Both studies were performed in an identical manner. Following an overnight fast, antipyrine (as 18 mg/kg) was given in 50 ml. of dilute orange juice; liquid and food being withheld for the ensueing 2 and 4 hours respectively. Smoking was not permitted for the first 4 hours of the test and the patients were usually ambulant during the two studies. Venous blood samples were withdrawn at 3, 5, 8, 11 and 24 hours after ingestion for estimation of plasma antipyrine.

The plasma half-life was calculated as previously described (page 48).

TABLE XXXXVIII

PARACETAMOL OVERDOSAGE — CLINICAL AND LABORATORY DETAILS

Case No.	Age (years)	Sex	Interval between overdosage and admission (hours)	Admission (and maximum) plasma paracetamol concentration (μg/ml)	Paracetamol half-life (hours)	Maximum ALT (units/l)	Maximum bilirubin (μmol/l)	Maximum prothrombin time ratio
1	18	F	4.75	220	3.1	274	12.8	1.3
2	25	M	15.0	108	9.7	9600	148.8	3.2
3	29	M	5.5	242	5.8	2760	27.6	2.9
4	38	F	144.0	-	-	7500	-	2.8
5	49	F	13.0	118	8.6	7000	121.1	2.0
6	20	M	16.5	104	5.5	1800	91.4	1.5
7	21	F	4.5	250	5.3	222	17.0	1.2
8	22	M	14.5	72	-	2820	31.9	1.7
9	43	M	9.75	247	5.8	3200	55.3	1.2
10	22	F	45.0	10	-	756	42.5	1.3
11	40	F	2.5	354	4.5	684	21.4	1.3
12	19	F	14.75	121	7.6	4020	116.9	2.4
13	26	M	5.5	142	4.6	411	29.8	1.4
14	29	F	15.5	49	5.8	5360	25.5	1.8
15	18	F	4.0	228	3.8	168	17.0	1.2
16	22	F	98.0	-	-	3200	23.4	1.2
17	20	M	4.0	286	4.1	52	19.1	1.4
Mean	27.1		24.5	170.1	5.79	2637	50.1	1.75
S.D.	9.6		38.5	98.1	1.86	2736	44.0	0.67

2. ANALYTICAL METHODS

a. Paracetamol

Paracetamol in plasma was estimated by gas-liquid chromatography (Prescott, 1971).

Phosphate buffer (1M, pH 7.4) was added to plasma and extracted with redistilled ethyl acetate containing N-butyryl-p-aminophenol as the internal standard. After centrifugation, the upper organic phase was removed and evaporated to dryness. Pyridine and acetic anhydride were added, the contents mixed, and the tubes incubated at 45° for 20 mins. 1 - 3 µl aliquots were injected into the gas chromatograph.

A Hewlett-Packard Model 402 gas chromatograph with a Nitrogen-sensitive flame ionization detector and a 2 ft long $\frac{1}{4}$ inch i.d. U-shaped glass tube column packed with 3% cyclohexane dimethanol succinate on 100/120 mesh Gaschrom Q was used with the column temperature 220°. The retention times of paracetamol and N-bytyryl-p-aminophenol were 3.4 and 4.5 mins. respectively.

Appropriate aqueous standards of paracetamol were run with the samples and unknown concentrations determined using the peak height ratios of drug to internal standard. The standard deviation of the assay over the range 5-500 µg/ml was 3.5%.

ii. Antipyrine

Antipyrine in plasma was estimated by the method of Brodie et al (1949). 2 ml. of plasma was added to 2 ml. of water and 2 ml of zinc reagent (containing 100 gm of $ZnSO_4$, with 40ml of 6N sulphuric acid dissolved in water and diluted to 1 litre). 2 ml. of 0.75 N NaoH was added and after shaking the mixture centrifuged. 3 ml. of clear supernatant fluid was withdrawn and 1 drop of 4N sulphuric acid added. The optical density was then read using a sphectrophotometer and the plasma concentrations calculated by reference to standard solutions.

3. RESULTS

The interval between ingestion of paracetamol and admission ranged from 2.5 to 144 hours (mean 24.5 hours); only 3 patients presenting more than 24 hours after the overdosage (Table XXXXVIII). The admission (and maximum) plasma paracetamol concentration was measured in 15 patients and ranged from less than 10 to 354 µg/ml (mean 170.1 µg/ml (Table XXXXVIII) In only 3 cases was the admission concentration less than 100 µg/ml.

The plasma paracetamol half-life was assessed in 13 of the patients (Table XXXXVIII) and ranged from 3.1 to 9.7 hours (mean 5.8 hours) being abnormally prolonged (greater than the mean ± 2 S.D. half-life in healthy subjects) in all patients. The maximum A.L.T. activity ranged from 52 to 9,600 U/l (mean 2639 U/l); all cases exceeding the upper limit of normal (40 U/l).

The initial antipyrine study was carried out a mean of 3.2 days after admission (range 1.5 - 7.0 days) (Table XXXXIX). In 9 of the 17 patients it was performed within 48 hours of admission.

The plasma antipyrine half-life in the initial study ranged from 8.8 to 32.7 hours (mean 20.6 hours). (Table XXXXIX) 10 of the 17 patients had an antipyrine half-life within the range found in healthy subjects (i.e. 11.6 ± 5.6 hours). In one patient (case no. 4) the antipyrine half-life was only 8.8 hours, despite a maximum A.L.T. value of 7500 U/l a few days previously and a value of 1152 U/l on the day the half-life was assessed. This patient was on long-term phenobarbitone therapy.

There were good correlations between the initial antipyrine half-life and the plasma paracetamol half-life ($r = 0.72$; $p < 0.01$) and the A.L.T. activity on the same day as the antipyrine study ($r = 0.59$; $p < 0.05$) (Fig. 15). Significant correlations were also noted between the antipyrine half-life and the serum bilirubin ($r = 0.52$; $p < 0.05$) and the prothrombin time ratio ($r = 0.53$; $p < 0.05$) on/

on the day of the antipyrine study but not with the alkaline phosphatase activity ($r = 0.08$; $p > 0.1$). There were, however, no significant correlations between the antipyrine half-life and the maximum A.L.T. values ($r = 0.18$; $p > 0.1$), maximum bilirubin ($r = 0.47$; $p > 0.05$) and maximum prothrombin time ratio ($r = 0.36$; $p > 0.1$).

The antipyrine half-life was again estimated in 8 of these patients 7 to 63 days (mean 17.5 days) after the initial study. In 5 patients (case nos. 8, 12, 13, 14 and 15) this second study was carried out 7 days after the first and in the remaining 3 the intervals were 21 days (cases 2 and 16) and 63 days (case 9). At this time all patients had made a complete clinical recovery from their overdose. However, their liver function tests had not all returned to normal at this time (Table XXXXX). Only 3 patients had A.L.T. values in the normal range; 3 patients having values of 588, 672 and 684 U/l, the mean value being 281 U/l. Two patients had a raised plasma bilirubin and one a raised alkaline phosphatase. The P.T.R. was only estimated in two patients at the time of the follow-up study, it being normal in both cases.

The mean plasma antipyrine half-life in the follow-up study was 13.3 hours (range 9.3 to 16.6 hours), (Table XXXXX). All of these values are in the range found in healthy subjects. However, in this repeat study, each half-life was shorter than in the initial study. The mean percentage reduction in the plasma half-life at the follow-up study compared with the initial study was 35.1% (range 2.4 to 55.7%). In this follow-up study there were no significant correlations between the antipyrine half-life and the A.L.T. activity ($r = 0.27$; $p > 0.1$), serum bilirubin ($r = 0.29$; $p > 0.1$) or alkaline phosphatase ($r = 0.19$; $p > 0.1$).

The mean volumes of antipyrine distribution were calculated as previously described (page 48) and were not significantly different at the initial and follow-up studies (0.54 and 0.62 l/kg respectively) ($t = 1.04$; $p > 0.05$).

TABLE XXXXIX

PARACETAMOL OVERDOSAGE. CLINICAL AND LABORATORY DETAILS

INITIAL ANTIPYRINE STUDY

Case No.	Interval between admission and initial anitpyrine study (days)	Antipyrine half-life (hours)	SGPT on same day (IU/1)	Bilirubin on same day (umol/1)	Alkaline phosphatase on same day (units/1)	Prothrombin time ratio on same day
1	1.5	14.0	128	8.5	69.2	1.2
2	5.0	25.4	2000	146.6	61.5	1.4
3	2.0	30.6	648	27.6	61.5	1.4
4	7.0	8.8	1152	17.0	138.4	1.0
5	4.5	27.5	2000	51.0	107.7	1.3
6	7.0	16.5	1800	19.1	84.6	-
7	1.5	15.3	97	17.0	69.2	1.0
8	2.5	28.8	1340	25.7	92.3	1.6
9	1.5	17.3	253	55.3	84.6	1.0
10	3.5	27.3	756	42.5	30.8	1.2
11	1.5	22.8	183	21.3	92.3	1.2
12	3.5	32.7	2780	116.9	146.1	-
13	1.5	15.6	411	29.8	76.9	1.3
14	2.0	20.4	504	21.3	61.5	1.7
15	2.0	12.6	129	17.0	92.3	1.2
16	6.0	22.6	912	17.0	61.5	1.2
17	2.0	12.1	52	14.9	69.2	1.3
MEAN	3.2	20.6	891	38.1	82.3	1.26
S.D.	2.0	7.2	829	37.8	28.6	0.19

TABLE XXXXX

PARACETAMOL OVERDOSAGE. CLINICAL AND LABORATORY DETAILS

FOLLOW-UP ANTIPYRINE STUDY

Case No.	Antipyrine half-life (hours)	SGPT on same day (IU/l)	Bilirubin on same day (µmol/l)	Alkaline phosphatase on same day (µmol/l)	Interval since initial study (days)
1	13.4	59	17.0	46.1	21
2					
3					
4					
5					
6					
7					
8	14.2	588	12.8	100	7
9	16.5	27	17.0	69.2	63
10					
11					
12	14.5	672	27.6	146.1	7
13	9.3	156	23.4	69.2	7
14	9.3	684	10.6	61.5	7
15	12.3	33	10.6	29.2	7
16	16.6	25	17.0	61.5	21
17					
MEAN	13.3	280.5	17.0	76.0	17.5
S.D.	2.8	308.0	6.0	29.9	19.4

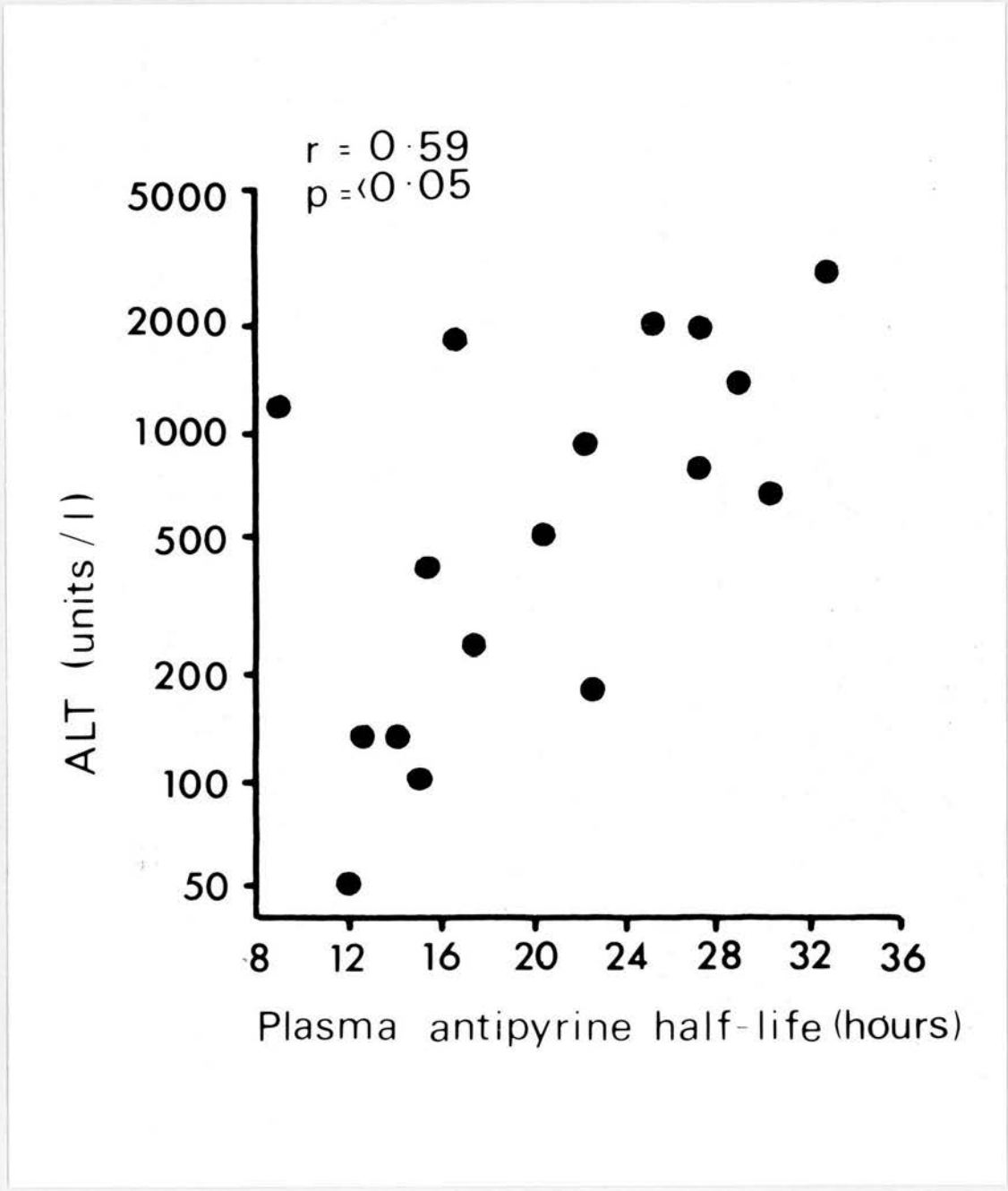

Fig. 15

Correlation between the plasma antipyrine half-life and the plasma ALT concentration on the same day in 17 patients with paracetamol induced acute hepatic necrosis.

4. DISCUSSION

Although there have been no other reports of the assessment of drug metabolising capacity in patients with acute hepatic necrosis following paracetamol overdosage similar assessments have been carried out in acute viral hepatitis (Blaschke et al., 1975; McHorse et al., 1975; Klotz et al., 1975; Burnett et al., 1976; Williams et al., 1976; Williams et al., 1977). In these studies, however, the severity of the hepatic necrosis - as judged by the A.L.T. activities - was generally less than in this study.

In this study the degree of necrosis varied from mild to severe; 10 of the 17 patients having maximum A.L.T. values in excess of 1000 U/l The initial antipyrine half-life was carried out a mean of 3.2. days after the overdosage, when all patients had an abnormally high A.L.T. concentration. At that time the mean antipyrine half-life was 20.6 hrs - although 7 of the 17 patients had a half-life in the range of healthy subjects. There was an excellent correlation between the antipyrine half-life and the A.L.T. activity on the same day and a lesser, though still significant, correlation with the serum bilirubin and P.T.R. There was no correlation, however, between the maximum A.L.T. activity and the antipyrine half-life. These significant correlations are not in agreement with studies of drug elimination in patients with acute viral hepatitis where no correlation was demonstrated between the plasma half-lives or clearances of pethidine (McHorse et al., 1975), diazepam (Klotz et al., 1975), antipyrine (Burnett et al., 1976), tolbutamide (Williams et al., 1977) andlignocaine (Williams et al., 1976) and any of the standard liver function tests. There may be two possible explanations for this discrepancy. Firstly, in some of these reported studies it is not clear if the A.L.T. concentration was estimated on the day the drug half-life was determined or whether the figure quoted represented a maximum concentration. If this were the case then the findings of this study would be in agreement with these other studies.

Secondly, in the patients with acute viral hepatitis the disease process may have been present for some period before the studies were undertaken whereas this was not the case in this study.

When the follow-up study was carried out a mean of 17.5 days after the initial study the antipyrine half-life in all 8 subjects was in the range of healthy subjects. There was a mean reduction in the antipyrine half-life at this follow-up study of 35.1% (range 2.4 - 55.7%), compared with the initial one. On this occasion, however, as in the other studies mentioned there was no correlation between the antipyrine half-life and any of the routine liver function tests. In these studies also, there was a return to normal rates of drug elimination when there was clinical and/or laboratory evidence of recovery from the hepatitis.

The prolonged drug half-lives are probably secondary to the reduction in the number of normally functioning hepatocytes. As liver blood flow has been shown to be normal in acute viral hepatitis (Preisig et al., 1976) it is unlikely that even for drugs with a high hepatic extraction ratio this mechanism contributes to the abnormal metabolism. It is of interest that the shortest antipyrine half-life in this study was seen in a patient (case no. 4) on long-term phenobarbitone; a drug known to shorten the antipyrine half-life (Hepner et al., 1977). Thus despite a maximum A.L.T. concentration of 7500 U/l a few days before the initial study and a concentration of 1152 U/l on the day of the study the patient's plasma antipyrine half-life was less than the mean of normal subjects at 8.8 hrs. This presumably reflects the microsomal induction in the remaining viable hepatocytes.

Drug metabolism may not, however, invariably be abnormal in actue hepatitis. Thus, Williams et al. (1977) found the tolbutamide plasma half-life and plasma clearance to be significantly less and greater respectively during the acute phase of viral hepatitis than following recovery. This was attributable to an increase in the plasma concentration/

concentration of the unbound drug, due to the action of displacing agents such as bilirubin thus making more of the drug available to the liver for metabolism. In addition, they noted that the clearance of tolbutamide, based on the unbound drug concentration, was not significantly different in the acute stages than on recovery.

In studies with phenytoin in acute viral hepatitis Blaschke et al. (1975) noted a similar phenomenon. Thus there was a 30% increase in the concentration of unbound phenytoin in the plasma during acute viral hepatitis compared with that on recovery. As a result of this phenytoin clearance was unaffected by acute viral hepatitis. Thus in this situation displacing agents such as bilirubin (Blaschke et al., 1975; Williams et al., 1977) may raise the concentration of unbound drug in the plasma and by thus making more available to the liver minimise the effect of the hepatitis on the rate of drug elimination.

In the present study there was no difference in the volume of distribution of antipyrine between the two studies. This finding is in agreement with those of McHorse et al. (1975), Burnett et al. (1976) and Williams et al. (1977) who noted that there was no significant differences in the volumes of distribution of pethidine, antipyrine and tolbutamide respectively between the acute phase of viral hepatitis and on clinical recovery.

5. SUMMARY

The antipyrine half-life was assessed in 17 patients with acute hepatic necrosis due to paracetamol poisoning a mean of 3.2 days after the overdosage. The antipyrine half-life was abnormally prolonged in10 of the patients; the mean value for all patients being 20.6 hours. There were significant correlations between the plasma antipyrine and plasma paracetamol half-lives and between the plasma antipyrine half-life and the A.L.T. and bilirubin concentrations and the P.T.R. on the day the study was performed. When a follow-up study was carried out 7 - 63 days later (mean 17.5 days) all patients had a half-life in the normal range; the % reduction compared with the initial study being 35%.

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APPENDIX

Published Papers.

Antipyrine, paracetamol, and lignocaine elimination in chronic liver disease

JOHN A H FORREST, N D C FINLAYSON, K K ADJEPON-YAMOAH, L F PRESCOTT

British Medical Journal, 1977, **1**, 1384-1387

Summary

The plasma half lives of antipyrine, paracetamol, and lignocaine given by mouth were measured in 23 patients with stable chronic liver diseases of varying severity. Fifteen patients received all three drugs and 19 at least two. The half life of paracetamol was abnormally prolonged in nine out of 17 patients (mean 2·9 hours, normal 2·0 hours), of antipyrine in 10 out of 19 patients (mean 30·4 hours, normal 12·0 hours), and of lignocaine in 19 out of 21 patients (mean 6·6 hours, normal 1·4 hours). Prolongation of the half lives of all three drugs was significantly correlated with an increase of the vitamin-K_1-corrected prothrombin time ratio and a reduction in serum albumin concentration. There was no correlation with serum bilirubin concentration or serum alanine aminotransferase activity. This suggests that impaired drug elimination was related to depressed hepatic protein synthesis. Considerable prolongation of the half life of one drug was invariably associated with delayed elimination of the others. The half life of ligno-

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caine, however, was always the most prolonged and was a highly sensitive indicator of hepatic dysfunction. The pharmacokinetic characteristics of a drug as well as the severity of liver disease should be taken into account when considering drug dosage in patients with chronic liver disease.

Introduction

The liver is an important site of drug metabolism, and serious toxicity may occur in patients with chronic liver disease prescribed drugs in normal dosage,[1] prolongation of the half life of many drugs extensively metabolised by the liver having been documented.[2–6] On the other hand, some investigators have reported a normal rate of elimination of some drugs in certain patients with chronic liver disease.[7–10] Possible reasons for these discrepancies are that insufficient attention has been given to the nature and severity of the underlying liver disease and to the pharmacokinetic characteristics of the drugs used.[11]

Antipyrine is commonly used to assess drug-metabolising capacity, and prolongation of its plasma half life has been reported in patients with decompensated liver disease.[12 13] Prolongation of the plasma half life of antipyrine is often assumed to be associated with corresponding changes in the elimination of other drugs, but this has not been examined in patients with chronic liver disease. Furthermore, in healthy volunteers the half life of antipyrine cannot always be correlated with the half lives of other drugs.[14–16]

Our aim was to compare the plasma half-lives of antipyrine, paracetamol, and lignocaine in the same patients with different forms of chronic stable liver disease of varying severity and to relate the findings to biochemical indices of liver function. Paracetamol and lignocaine were chosen because, unlike antipyrine, they are widely used in clinical practice and have different primary routes of metabolism and different pharmacokinetic characteristics.

Patients and methods

We studied 23 patients admitted for investigation and treatment of chronic liver disease. Informed consent was obtained from all. Table I gives the clinical details and diagnoses, which in all but three patients were established by biopsy or necropsy. The following indices of liver function were measured before the drugs were given: serum bilirubin and albumin concentrations, serum alanine aminotransferase (SGPT) and alkaline phosphatase activities, and the prothrombin time ratio (PTR). The respective normal values are 2-17 μmol/l (0·12-1·0 mg/100 ml), 36-47 g/l, 10-40 U/l, 40-100 U/l, and 1·3 or less. If the PTR was over 1·4, vitamin K_1 (10 mg intramuscularly) was given on two successive days, the PTR remeasured, and this vitamin-K_1-corrected PTR used.

A complete drug history was taken, and whenever possible all drugs

TABLE I—*Clinical and laboratory details of patients studied*

Case No	Age (years)	Sex	Diagnosis	Bilirubin (μmol/l)	SGPT (U/l)	Alkaline phosphatase (U/l)	Albumin (g/l)	Prothrombin time ratio	Antipyrine half life (h)	Paracetamol half life (h)	Lignocaine half life (h)
1	45	M	Alcoholic cirrhosis	17·1	14	119	43	1·0			4·3
2	49	M	" "	12·0	16	112	44	1·2	11·5	1·5	1·8
3	51	M	" "	90·6	36	350	36	1·3	41·0	2·5	7·5
4	60	M	" "	23·9	21	147	33	1·4	41·0	3·3	4·5
5	29	M	" "	51·3	35	77	30	1·3	15·7	1·8	2·1
6	68	M	" "	30·8	43	315	45	1·2			2·3
7	59	M	" "	37·6	21	84	33	1·6	37·0	2·9	9·0
8	48	F	" "	39·3	22	161	25	1·4	27·0	3·3	6·0
9	52	F	" "	39·3	9	112	28	1·6	31·2	4·3	5·6
10	44	M	" "	99·2	38	154	26	2·0			7·1
11	60	F	" "	114·6	24	168	25	1·9	49·0	7·0	12·4
12	60	M	" "	53·0	43	315	24	1·9	24·0	2·8	
13	55	M	" "	70·1	35	280	22	1·8			16·2
14	41	F	Cryptogenic cirrhosis	12·0	22	182	42	1·0	4·9	1·5	1·8
15	27	F	" "	18·0	101	350	36	1·2	15·5	3·7	6·1
16	67	F	Chronic active hepatitis	95·8	200	119	31	1·3	23·7	2·4	4·1
17	54	F	" " "	47·9	103	329	22	1·4	56·0	4·4	13·2
18	28	F	" " "	201·8	21	1190	21	3·6	137·0		19·0
19	54	F	Primary biliary cirrhosis	124·8	106	595	31	1·0	15·0	3·0	
20	43	F	" " "	430·9	21	2625	32	1·1	12·3		2·6
21	56	F	" " "	42·8	48	560	27	1·3	11·0	2·0	3·2
22	67	M	Nodular transformation	17·1	17	98	39	1·0	9·8	2·0	4·6
23	29	F	Sclerosing cholangitis	248·0	126	1085	34	1·2	14·0	1·5	5·0
Mean ± SE of mean	49·8 ± 2·6			83·4 ± 20·0	48·8 ± 9·8	414 ± 118	31·7 ± 1·5	1·5 ± 0·1	30·3 ± 6·8	2·9 ± 0·3	6·6 ± 1·1

Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml.

were stopped before the studies began. Ten patients had been taking drugs regularly: in case 4 bendrofluazide and spironolactone; in case 8 spironolactone and protriptyline; in case 9 bendrofluazide; in cases 7, 13, and 16 frusemide and spironolactone; in case 11 spironolactone; in cases 16 and 18 prednisolone; in case 20 cholestyramine and chlorpheniramine; and in case 21 pentobarbitone.

At the time of study all patients were stable in their optimal clinical state and none was in cardiac failure. Only one patient (case 13) had a raised blood urea concentration. Five patients (cases 8, 11, 12, 13, and 18) had ascites, and six (cases 2, 4, 7, 9, 13, and 21) oesophageal varices. Two patients (cases 15 and 23) had previously undergone portosystemic shunt operations, the shunts being judged patent by a continuing absence of varices.

The test drugs were administered consecutively two to three days apart over 7-10 days and usually in the sequence lignocaine, antipyrine, paracetamol. The studies followed a similar pattern. After an overnight fast each drug was administered with 40 ml of water in the following dosage: lignocaine hydrochloride 400 mg (tablets); antipyrine 18 mg/kg (in solution); paracetamol 1·5 g (tablets). Food and fluids were withheld for two hours after ingestion. At least five blood samples were taken for estimation of drug concentrations over 24, 48, and 9 hours respectively.

The plasma was separated and stored frozen until the drug concentrations were determined by gas-liquid chromatography.[17 19] Half lives of the drugs were calculated from the linear regression of the logarithms of the plasma concentrations against time by using the method of least squares. The plasma half lives of these three drugs in healthy people were reported previously.[20-22] Abnormal prolongation of half life was defined as greater than 2 SD beyond the mean value in normal people.

Results

The mean plasma half life of each drug was prolonged in patients with liver disease compared with the mean values in healthy people (table II). The half life of lignocaine was prolonged to a much greater extent (371 %) than that of antipyrine (153 %) or paracetamol (45 %).

The half life of lignocaine was abnormally prolonged in 19 out of 21 patients, of antipyrine in 10 out of 19 patients, and of paracetamol in

TABLE II—*Mean half lives of paracetamol, antipyrine, and lignocaine in plasma (± SD) in healthy people and patients with chronic liver disease*

	Paracetamol half life (h)	Antipyrine half life (h)	Lignocaine half life (h)
Patients with chronic liver disease ..	2·9 ± 0·3	30·3 ± 6·8	6·6 ± 1·1
Healthy people ..	2·0 ± 0·4*	12·0 ± 3·5†	1·4 ± 0·26‡
% Difference	45	153	371

*See ref [22]. †See ref [21]. ‡See ref [20].

nine out of 17 patients. There were significant correlations between the half lives of all three drugs ($r = 0·73$; $P < 0·01$). Comparison of the plasma half lives of the drugs with the liver function values showed

significant correlations between the half life of each drug and the serum albumin concentration ($r > 0.58$; $P < 0.01$) and PTR ($r > 0.64$; $P < 0.01$) but not with serum bilirubin ($r < 0.16$; $P > 0.05$), SGPT ($r < 0.17$; $P > 0.05$), or alkaline phosphatase ($r < 0.21$; $P > 0.05$).

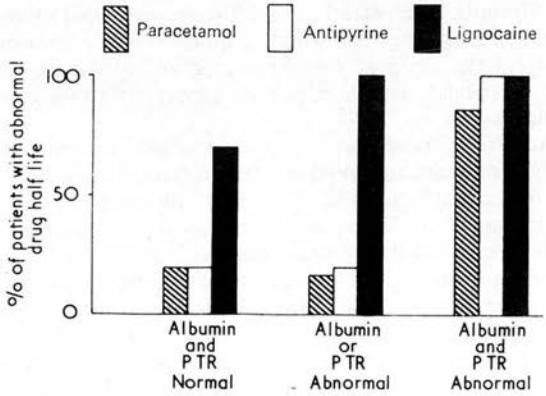
In 13 patients either the serum albumin concentration or the PTR or both were normal. Two out of 11 of these patients had a prolonged half life of antipyrine, and two out of 10 a prolonged half life of paracetamol. In no instance was the increase pronounced (table III). In the other 10 patients both the serum albumin concentration and the PTR were abnormal; among these patients, six out of seven had a prolonged half life of paracetamol, and all eight tested a prolonged half life of antipyrine. In these patients the prolongation was considerable (table III).

TABLE III—*Mean percentage increase in drug half lives in relation to serum albumin concentration and prothrombin time ratio (PTR)*

	Albumin and PTR normal	Albumin or PTR abnormal	Albumin and PTR abnormal
Paracetamol	12	7	100
Antipyrine	38	27	319
Lignocaine	190	143	638

The half life of lignocaine was prolonged in five out of seven patients with a normal albumin concentration and PTR, but in all patients in whom one or both of these values were abnormal lignocaine elimination was abnormally slow (see figure). In all instances prolongation of the lignocaine half life was considerable (table III). When both the serum albumin and PTR were abnormal, lignocaine was eliminated at only one-sixth of the normal rate.

In the patients known to have taken compounds causing microsomal enzyme induction the drug half lives were not significantly different from those of others with a similar degree of liver dysfunction as assessed by routine liver function tests.



Relation of serum albumin concentration and prothrombin time ratio (PTR) to frequency of abnormal plasma half lives of paracetamol antipyrine, and lignocaine.

Discussion

Since many drugs are extensively metabolised by the liver it is important to know whether their elimination is abnormally slow in patients with chronic liver disease so that a reduction in dosage can be made to reduce the risk of accumulation and toxicity. Although the rate of elimination of antipyrine[12 13] is reduced in patients with chronic liver disease, simultaneous comparisons with other drugs do not seem to have been made. To ascertain whether the elimination of individual drugs might be different we have studied the rates of elimination of three drugs, each having a different primary route of metabolism (antipyrine, hydroxylation; paracetamol, conjugation; lignocaine, N-dealkylation) and different pharmacokinetic properties (hepatic-extraction ratios: antipyrine 0·03, paracetamol 0·15, lignocaine 0·70), in patients with different forms of stable chronic liver disease.

The plasma half life of lignocaine was prolonged to a much greater extent than that of antipyrine, and paracetamol was affected least. Although there was a good correlation between the plasma half lives of all three drugs, minor prolongation of the antipyrine half life could be associated with severely impaired elimination of lignocaine and a normal paracetamol half life. Thus the half life of antipyrine is a poor indicator of the ability of patients with chronic liver disease to eliminate other drugs. The half lives of paracetamol and antipyrine were increased in 20% of patients with a normal serum albumin concentration or PTR, although the mean increases over normal, of 10% and 33% respectively, are of little clinical importance in respect of the drug dosage that might be prescribed. Even when these two indices of liver function were normal the mean rate of lignocaine elimination was only 50% of normal, some 70% of patients having a prolonged half life. In contrast the half life of only one drug was normal in patients with an abnormal albumin concentration and PTR. Regardless of the serum albumin concentration or PTR, paracetamol elimination was always least affected, which might have been due to conjugation of the drug at extrahepatic sites such as the gastrointestinal mucosa, which is rich in glucuronyl transferase and aryl sulphatase.

Lignocaine elimination, in contrast, was always the most severely depressed, and in those patients with an abnormal serum albumin concentration and PTR was eliminated at only 16% of the normal rate. There are several possible explanations for this. Hepatic blood flow is often decreased in cirrhosis by portosystemic shunting,[23] and this might have a much greater effect on the clearance of drugs with a high hepatic extraction ratio such as lignocaine than on drugs with a low ratio such as paracetamol or antipyrine. This is supported by the greatly prolonged half life of lignocaine in patients with cardiac failure.[24] Branch *et al*[12] found no difference in the half life of antipyrine between patients with and without evidence of portosystemic

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shunting who had liver disease of similar severity, suggesting that reduced liver blood flow has little effect on the clearance of antipyrine. On the other hand, treatment with inducing agents such as phenobarbitone greatly reduced the plasma half life of antipyrine, suggesting that enzyme activity in the liver cell is a major determinant of the hepatic clearance of drugs with a low hepatic extraction ratio. In addition, the differences observed in the half lives of the different drugs could be due in part to the varying activities of the different enzyme systems.

Our findings do not allow a distinction to be made between selective impairment of the different drug metabolising enzymes and reduction in hepatic blood flow as an explanation for the observed differences in the half lives of antipyrine, paracetamol, and lignocaine. For drugs with a high hepatic extraction ratio, however, liver blood flow may be more important than enzymatic activity. Whatever the precise mechanisms it is clear that the elimination of some drugs is grossly abnormal in many patients with chronic liver disease. Often there may be severe depression of metabolism resulting in rapid accumulation and serious or fatal toxicity when conventional doses are used, patients with a low serum albumin concentration and a prolonged PTR being most at risk. This should be borne in mind when prescribing drugs for patients with chronic liver disease. It would seem appropriate to start with a reduced dosage when the drug is mainly metabolised by the liver, has a high hepatic extraction ratio, and is being given to patients with severe liver disease.

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normal Drug Metabolism after Barbiturate and racetamol Overdose

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metabolizing capacity has been assessed by serial rements of the plasma antipyrine half life in 11 patients evere barbiturate intoxication and in 17 patients with hepatic necrosis due to paracetamol overdosage. Drug olism was strikingly enhanced after barbiturate over-, and this effect was still present six weeks later. In st the antipyrine half life was greatly prolonged in patients with paracetamol-induced acute hepatic necrosis but returned to normal or near-normal values within seven to 21 days.

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Introduction

Long-term administration of hypnotics such as barbiturates, glutethimide, and diphenhydramine-methaqualone (Mandrax) can cause stimulation of hepatic microsomal enzyme activity and thereby enhance the rate of metabolism of many drugs (MacDonald *et al.*, 1969; Stevenson *et al.*, 1972; Breckenridge *et al.*, 1973 a). This stimulatory effect develops over three to four weeks and persists for a similar period after the inducing drug is discontinued. The barbiturates produce a dose-related induction of microsomal enzymes in man (Breckenridge *et al.*, 1973 a), and marked acceleration of drug metabolism might be expected after severe overdosage with these drugs since this probably represents the maximum stimulus for induction likely to be encountered in practice. On the other hand, drug metabolism is likely to

be seriously impaired in patients with acute hepatic injury, such as that caused by paracetamol overdosage (Prescott and Stevenson, 1973; Simpson and Stewart, 1973). It is clearly important to establish the effects of overdosage on drug metabolism so that any drugs required subsequently can be given in appropriate dosage.

In this report we describe studies of drug metabolism in patients after severe barbiturate and paracetamol poisoning. The plasma antipyrine half life was used as an index of hepatic drug metabolism and studies were carried out at intervals after overdosage to establish the time course of the changes produced.

Patients and Methods

BARBITURATE OVERDOSAGE

Studies were carried out on 11 patients admitted to the Regional Poisoning Treatment Centre because of intoxication with short-acting or medium-acting barbiturates. Nine patients were in grade IV coma and two (cases 7 and 8) were in grade III coma (Matthew and Lawson, 1970). The ingestion of other drugs commonly taken in overdosage was excluded by a urine screening technique but one patient (case 10) had also taken alcohol (blood alcohol on admission 173 mg/100 ml). The clinical details are summarized in table 1. None of the patients had a history of previous liver disease or chronic alcoholism and there was no clinical evidence of cardiac or renal disease. Two patients (cases 1 and 5) were addicted to barbiturates, four (cases 2, 9, 10, and 11) took them regularly as a hypnotic, and one (case 11) had also taken prednisolone 5-10 mg daily for some years because of asthma.

Treatment consisted in routine intensive supportive therapy with gastric lavage when indicated (Matthew and Lawson, 1970). Intermittent positive-pressure ventilation was used in cases 1, 2, 3, 4, 10, and 11 for a mean period of 31·2 All patients recovered without complications.

The plasma antipyrine half life was measured on th morning that the patient was conscious and able to take (study 1). The mean interval between admission and st was 51·2 hours (range 20-87 hours). In eight patients th pyrine half life was measured again a week later (study in five the test was repeated after another five weeks (stu The patients remained in hospital between studies 1 and did not receive any drugs other than ampicillin.

Plasma barbiturate concentrations were usually estima intervals of six to eight hours from admission until the pletion of study 1. The drugs were extracted into chlor and estimated by direct gas-liquid chromatography on columns (Street, 1969).

PARACETAMOL OVERDOSAGE

The plasma antipyrine half life was measured in 17 pa with acute hepatic necrosis after paracetamol overdosag table II). Apart from one patient (case 20), who was a cl alcoholic, none was known to have pre-existing liver d An epileptic patient (case 15) was taking phenobarbiton three others (cases 13, 23, and 26) claimed to have bee ing fluphenazine with orphenadrine, Minovlar (nor terone), and nitrazepam respectively before admission. patients had taken alcohol at the time of overdosage. from two patients (cases 13 and 23) who received fresh plasma no treatment was required. The severity of the tic necrosis was assessed by daily measurement of the thrombin time, serum alanine aminotransferase (SGPT tivity, and bilirubin concentration. Plasma paracetamol centrations were determined on admission in 15 cases, 14 cases blood samples were taken at intervals for up

TABLE I—*Barbiturate Overdosage. Clinical and Laboratory Details*

Case No.	Age (Years)	Sex	Barbiturate	Maximum Plasma Concentration (μg/ml)	Total Duration of Coma (Hours)	Antipyrine Half Life (Hour		
						Study 1	Study 2	St
1	49	F.	Cyclobarbitone	142	30	6·95	4·9	
2	52	F.	Amylobarbitone	66	59	5·3	3·5	
3	24	F.	Amylobarbitone, quinalbarbitone*	76, 52	80	8·0	7·4	1
4	67	F.	Amylobarbitone	40	44	7·6	3·7	
5†	44	M.	Butobarbitone	118	18	7·0		
	44	M.	Butobarbitone	100	30	4·9	3·3	
6	29	M.	Amylobarbitone, quinalbarbitone*	17, 15	48	5·1	3·9	
7	26	M.	Pentobarbitone	27	27	8·6	6·5	
8	22	F.	Amylobarbitone, quinalbarbitone*	16, 13	33	4·8	5·4	
9	69	F.	Pentobarbitone	26	43	3·4		
10	43	F.	Quinalbarbitone	67	44	4·8		
11	41	F.	Amylobarbitone, quinalbarbitone*	34, 32	57	5·7		
Mean ± S.E.	42·4 ± 4·9			70·1 ± 11·4	42·8 ± 4·9	6·0 ± 0·5	4·8 ± 0·5	7·

*Tuinal. †This patient took butobarbitone in overdosage on two occasions.

TABLE II—*Paracetamol Overdosage. Clinical and Laboratory Details*

Case No.	Age (Years)	Sex	Paracetamol Half Life (Hours)	Maximum SGPT (IU/l)	Maximum Bilirubin (mg/100 ml)	Maximum Prothrombin (Ratio)	Interval between Admission and Initial Antipyrine Study (Days)	Initial Study		Follow-up St	
								Antipyrine Half Life (Hours)	SGPT on Same Day (IU/l)	Antipyrine Half Life (Hours)	SG Sa
12	18	F.	3·1	274	0·6	1·3	1·5	14·0	128		
13	25	M.	9·7	9600	7·0	3·2	5·0	25·4	>2000	13·4	
14	29	M.	5·8	2760	1·3	2·9	2·0	30·6	648		
15	38	F.		7500			7·0	8·8	1152		
16	49	F.	8·6	>2000	5·7	2·0	4·5	27·5	>2000		
17	20	M.	5·5	1800	4·3	1·5	7·0	16·5	1800		
18	21	F.	5·3	222	0·8	1·2	1·5	15·3	97		
19	22	M.		2820	1·5	1·7	2·5	28·8	1340	14·2	
20	43	M.	5·8	3200	2·6	1·2	1·5	17·3	253	16·5	
21	22	F.		756	2·0	1·3	3·5	27·3	756		
22	40	F.	4·5	684	1·0	1·3	1·5	22·8	183		
23	19	F.	7·6	4020	5·5	2·4	3·5	32·7	2780	14·5	
24	26	M.	4·6	411	1·4	1·4	1·5	15·6	411	9·3	
25	29	F.	5·8	5360	1·2	1·8	2·0	20·4	504	9·6	
26	18	F.	3·8	168	0·8	1·2	2·0	12·6	129	12·3	
27	22	F.	6·8	3200	1·1	1·2	6·0	22·6	912	16·6	
28	20	M.	4·1	52	0·9	1·4	2·0	12·1	52		
Mean ± S.E.	27·1 ± 2·3		5·8 ± 0·5	2639 ± 664	2·3 ± 0·5	1·7 ± 0·2	3·2 ± 0·5	20·6 ± 1·8	891 ± 201	13·3 ± 1·0	2

for estimation of the plasma paracetamol half life. Paracetamol was estimated using a gas-liquid chromatographic method (Prescott, 1971).

In patients with mild to moderate liver damage the antipyrine half life was usually measured within two days of admission, but in patients with severe hepatic necrosis administration of antipyrine was delayed until there was clinical or biochemical evidence of recovery (table II). The antipyrine half life was determined again in eight patients who could be followed up. In five patients the second study was carried out seven days after the first, and in the remaining three the intervals were 21 days (cases 13 and 27) and 63 days (case 20). Plasma antipyrine was measured as described by O'Malley et al. (1971), though in some patients with liver damage additional blood samples were taken for up to 24 hours. The statistical significance of changes in antipyrine half life and volumes of distribution was assessed using Student's *t* test.

Results

BARBITURATE OVERDOSAGE

The mean maximum plasma barbiturate concentration was 30 μg/ml and the men duration of unconsciousness was 30 hours (table I). On the day that the patients regained consciousness (study 1) the mean (± S.E.) antipyrine half life was only 6·0 ± 0·5 hours compared with 12·0 ± 0·5 hours previously observed in healthy adults aged 20 to 50 years (O'Malley *et al.*, 1971). One week later (study 2) the antipyrine half life had shortened to 4·8 ± 0·5 hours, the lowest individual value being 3·3 hours. Six weeks after the overdose (study 3) the mean antipyrine half life had increased but was still abnormally short at 7·7 ± 0·8 hours (fig. 1). The mean antipyrine half life in all three studies differed significantly from normal and from each other ($P < 0.005$). There were no significant differences between the apparent volumes of antipyrine distribution in the three studies (0·60, and 0·63 l./kg respectively).

There was a progressive increase in the rate of elimination of barbiturates from the plasma during recovery in nine patients; these findings are also in keeping with stimulation of hepatic microsomal enzymes during the recovery phase. An example is shown in fig. 2. The mean plasma barbiturate half life for the whole group during the first 24 hours after admission was 25·1 ± 3·5 hours but this had fallen to 10·7 ± 1·1 hours on the day that the first antipyrine study was carried out. At that time there was no statistically significant correlation between the barbiturate and antipyrine half lives ($r = 0.37$; $P > 0.2$).

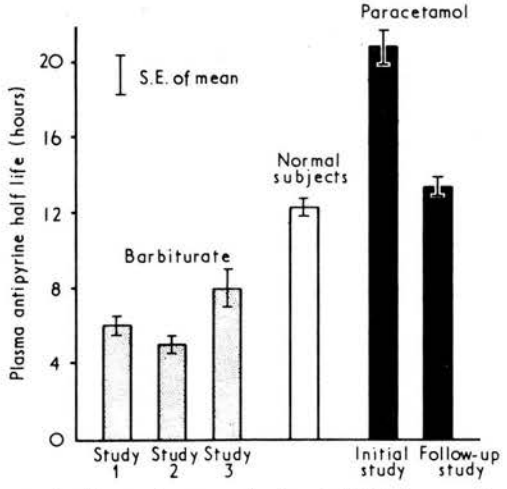

FIG. 1—Mean plasma antipyrine half life in normal subjects and in patients after barbiturate and paracetamol overdosage.

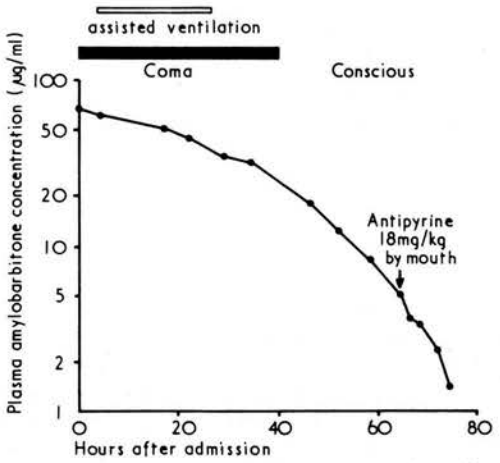

FIG. 2—Increasing rate of disappearance of amylobarbitone from plasma in case 2 during recovery from amylobarbitone intoxication.

PARACETAMOL OVERDOSAGE

The mean interval between ingestion of paracetamol and admission was 8·6 ± 1·5 hours, the mean plasma paracetamol concentration on admission being 189 ± 24 μg/ml. The paracetamol half life was more than four hours in 12 of the 14 patients in whom it was estimated (Prescott *et al.*, 1971). SPGT activity exceeded the upper limit of normal (35 IU/l.) in all 17 cases, the mean maximum value being 2,639 IU/l. (table II). At the time of the initial and follow-up antipyrine studies the mean SPGT levels were 891 and 280 IU/l. respectively.

The mean plasma antipyrine half life in the initial study was 20·6 hours (fig. 1) and there were highly significant correlations between the antipyrine half life and the SGPT activity on the same day ($r = 0.92$) (fig. 3) and the plasma paracetamol half life ($r = 0.72$). Similar but less striking correlations were observed between the antipyrine half life and the serum bilirubin ($r = 0.52$) and prothrombin time ratio ($r = 0.53$) determined on the day of the antipyrine test. In only one patient (case 15) was the antipyrine half life shorter than normal (8·8 hours), but this patient was on long-term phenobarbitone therapy.

When the antipyrine study was repeated in eight patients after an interval of seven to 63 days the mean half life had fallen to 13·3 hours (fig. 1). On this occasion there was no sig-

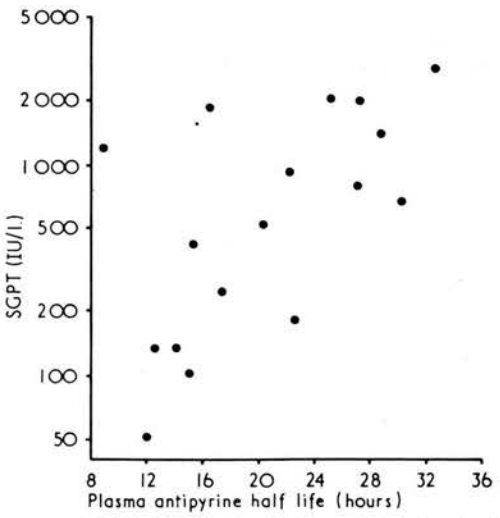

FIG. 3—Correlation between plasma antipyrine half life and SGPT measured on same day in patients with paracetamol-induced hepatic necrosis ($r = 0.92$).

nificant correlation with SGPT activity, and in three patients with SGPT values ranging from 588 to 684 IU/l. the antipyrine half life ranged from 9·6 to 14·5 hours (table II). The mean volumes of antipyrine distribution at the initial and follow-up studies were 0·54 and 0·62 l./kg. A paired t test carried out on the data from the eight patients studied twice showed no statistically significant difference ($t = 1·04$; $P > 0·05$).

Discussion

The plasma antipyrine half life is widely used as a measure of drug-metabolizing capacity in man, and several investigators have observed changes after treatment with drugs which cause induction or inhibition of microsomal drug-metabolizing enzymes (Kolmodin *et al.*, 1969; Vessell and Page, 1969; Kampffmeyer, 1971; O'Malley *et al.*, 1972). Though the rate of elimination of antipyrine does not always correlate with the plasma half life of other drugs metabolized by the liver microsomal enzymes (Kadar *et al.*, 1973) there seems little doubt that in the present study drug metabolism was enhanced after severe barbiturate intoxication and impaired in patients with acute hepatic necrosis due to paracetamol overdosage. Though previous work (Remmer, 1962) suggested that barbiturate poisoning may stimulate hepatic drug metabolism no detailed assessment of this finding seems to have been carried out.

Significant enzyme induction had probably occurred by the time our barbiturate patients regained consciousness, since both the barbiturate and antipyrine half lives were abnormally short at that time. For example, the plasma half life of amylobarbitone in healthy adults is about 24 hours (Balasubramaniam *et al.*, 1970) but in some of our patients it had fallen to six to 12 hours on recovery. Progressive shortening of the plasma barbiturate half life during recovery from severe intoxication does not seem to have been described previously. Though this was probably due largely to enzyme induction the initial rate of disappearance of barbiturate from the plasma could have been slowed by factors such as continuing gastrointestinal absorption, hypothermia, hypotension, hypoxia, and, perhaps, dose-dependent metabolism. In addition the metabolism of barbiturate may have been enhanced by increased production of cortisol during recovery (Collins *et al.*, 1971) since the elimination of antipyrine in normal subjects can be increased by infusion of physiological doses of hydrocortisone (Breckenridge *et al.*, 1973 b).

The plasma antipyrine half life was even shorter seven days after the patients regained consciousness and the metabolism of the drug was still abnormally rapid six weeks after the overdosage. Thus for at least six weeks after severe barbiturate poisoning drugs which are primarily inactivated by hepatic microsomal enzymes may have to be given more often and in increased dosage in order to produce the desired therapeutic effects.

In contrast the metabolism of antipyrine was impair the patients with paracetamol-induced acute hepatic nec Prolongation of the antipyrine half life was related t extent of liver damage as shown by the paracetamol hal SGPT activity, serum bilirubin, and the prothrombin ratio. The only patient with an antipyrine half life o than 12 hours was an epileptic in whom previous cons tion of phenobarbitone had presumably caused micro enzyme induction. The antipyrine half life in patient ceiving anticonvulsants may be reduced to four to five (I. H. Stevenson, unpublished).

Drug metabolism apparently returned to normal v seven to 21 days of severe paracetamol overdosage thoug SGPT activity was still raised in some patients. Thus d this period it is possible that other drugs might have given in reduced dosage to prevent cumulation and to Combined overdosage of paracetamol and hypnotics is ticularly dangerous, and prolonged coma due to impai of barbiturate metabolism has been observed in patients t a combination of barbiturates and paracetamol in overd (Prescott and Stevenson, 1973; Simpson and Stewart,

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Paracetamol Metabolism in Chronic Liver Disease

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Summary. The plasma concentrations and urinary excretion of paracetamol and its glucuronide, sulphate, cysteine and mercapturic acid conjugates were measured in eight normal subjects, eight patients with mild liver disease and seven patients with severe liver disease following an oral dose of 1.5 g of paracetamol. The mean plasma paracetamol half-life was similar in normal subjects (2.43 h ± 0.19) and those with mild liver disease (2.16 h ± 0.54) but was significantly prolonged in all patients with severe liver disease (4.25 h ± 1.15: $p = < 0.001$). Prolongation of the paracetamol half-life was related to reduced plasma albumin and increased prothrombin time. The mean ratios of plasma concentrations of unchanged paracetamol to paracetamol glucuronide and sulphate were significantly greater in patients with severe liver disease than the normal subjects. There were no significant differences in the overall 24-h urinary excretion of paracetamol and its glucuronide, sulphate, cysteine and mercapturic acid conjugates in the three groups. The glutathione conjugation of paracetamol did not seem to be impaired in patients with severe liver disease as evidenced by the production of normal amounts of the cysteine and mercapturic acid conjugates. There is thus no evidence that they are at increased risk of hepatotoxicity when given a single therapeutic dose of paracetamol.

Key words: paracetamol, liver disease; half-life, plasma metabolites, urinary metabolites

Although in therapeutic doses paracetamol is a safe and effective analgesic, in overdosage it can cause severe hepatic necrosis [1–3]. Hepatotoxicity is related to the formation of a minor but highly reactive intermediate metabolite of paracetamol and to depletion of hepatic glutathione. The latter compound protects the liver cells by combining preferentially with the toxic metabolite to form cysteine and mercapturic acid conjugates which are excreted in the urine [4–7]. Little is known of the metabolism of paracetamol or the capacity for glutathione conjugation of this drug in patients with chronic liver disease and the risk of further liver damage when these patients take therapeutic doses of the drug is unknown. Although paracetamol metabolism is abnormal in some patients with chronic liver disease [8–10] there has been no detailed investigation of its metabolism in such patients. The purpose of this study was to measure the plasma concentrations and urinary excretion of paracetamol and its metabolites following a therapeutic dose in patients with chronic liver disease. Particular attention was given to the excretion of the cysteine and mercapturic acid conjugates since abnormal production of these metabolites might indicate an increased risk of hepatotoxicity in such patients.

Patients and Methods

Fifteen patients with chronic liver disease were studied with informed consent. Their weights ranged from 45 to 77 kg (mean 61.8 kg). Table 1 gives the clinical details and diagnoses which were established by liver biopsy or autopsy in all but three patients. Prior to the study the following laboratory tests were performed: plasma urea, serum bilirubin and albumin concentrations, alanine aminotransferase (A. L. T.) and alkaline phosphatase activities and prothrombin time ratio (P. T. R.). The respective normal values are 2.5–6.6 mmol/l, 2–17 μmol/l, 36–47 g/l, 10–40 IU/l, 40–100 IU/l and 1.3 or less.

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Table 1. Clinical and laboratory details of patients studied

Case no.	Age (years)	Sex	Diagnosis	Bilirubin (mmol/l)	A.L.T. (u/l)	Alk. phos. (u/l)	Albumin (g/l)	Prothrombin time ratio	Paracetamol half-life (hours)
1	49	M	Alcoholic cirrhosis	12.0	16	112	44	1.2	1.6
2	51	M	Alcoholic cirrhosis	90.6	36	350	36	1.3	2.9
3	29	M	Alcoholic cirrhosis	51.3	35	77	30	1.3	1.8
4	41	F	Cryptogenic cirrhosis	12.0	22	182	42	1.0	1.7
5	67	F	Chronic active hepatitis	95.8	200	119	31	1.3	3.1
6	54	F	Primary biliary cirrhosis	124.8	106	595	31	1.0	2.2
7	56	F	Primary biliary cirrhosis	42.8	48	560	27	1.3	2.2
8	67	M	Nodular transformation	17.1	17	98	39	1.0	1.9
9	27	F	Cryptogenic cirrhosis	18	101	350	36	1.2	4.0
10	59	M	Alcoholic cirrhosis	37.6	21	84	33	1.6	3.6
11	48	F	Alcoholic cirrhosis	39.3	22	161	25	1.4	3.5
12	52	F	Alcoholic cirrhosis	39.3	9	112	28	1.6	3.7
13	60	F	Alcoholic cirrhosis	114.6	24	168	25	1.9	6.5
14	60	M	Alcoholic cirrhosis	23.9	21	147	35	1.4	3.3
15	54	F	Chronic active hepatitis	47.9	103	329	22	1.4	5.1

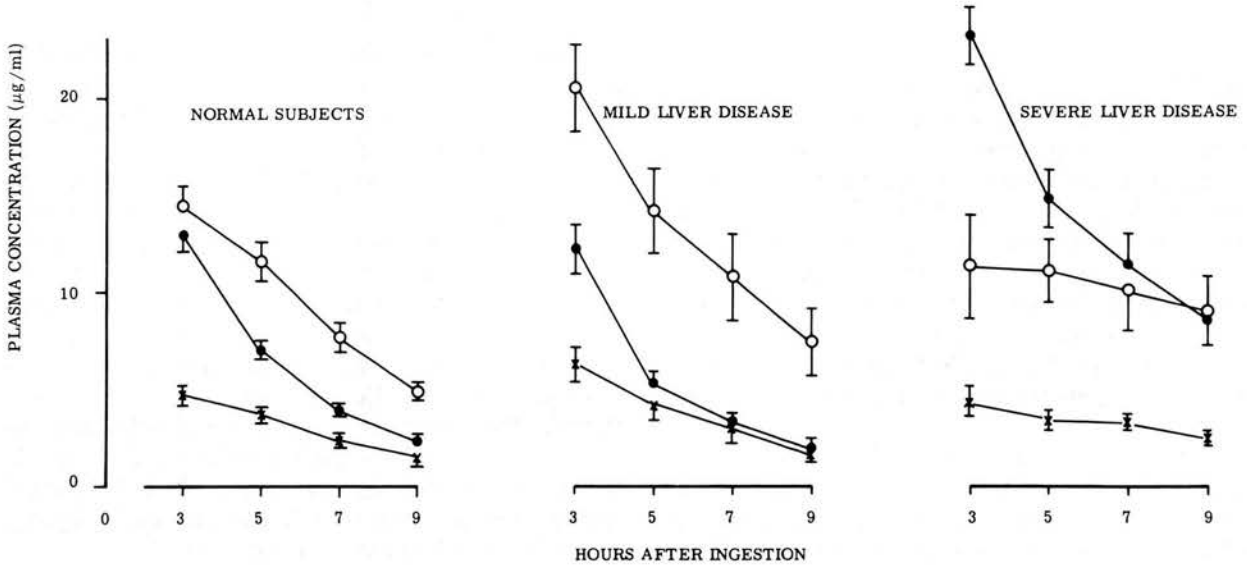

Fig. 1. Plasma concentrations of paracetamol (●) and its glucuronide (○) and sulphate (×) conjugates in normal subjects and patients wit mild and severe chronic liver disease after a single oral dose of 1.5 g. Concentrations of conjugates are expressed as paracetam equivalents (means ± S. E.)

Table 2. 24-h urinary recovery (as % of dose) of paracetamol and metabolites following 1.5 g of oral paracetamol

	Paracetamol	Sulphate	Glucuronide	Cysteine	Mercapturate	% of dose recovered	Urine vol. (ml)
Normal Subjects (N=8)	3.7 ± 0.2	33 ± 1.2	54 ± 1.4	3.8 ± 0.1	4.8 ± 0.2	92 ± 0.6	1163 ± 63
Mild liver disease (N=8)	2.7 ± 0.3	29 ± 1.9	59 ± 2.3	4.4 ± 0.6	4.3 ± 0.7	81 ± 3.1	1626 ± 222
Severe liver disease (N=7)	4.6 ± 0.8	35 ± 3.1	50 ± 3.7	4.2 ± 0.9	4.2 ± 0.6	84 ± 5.5	1397 ± 323

Values are means ± S.E.

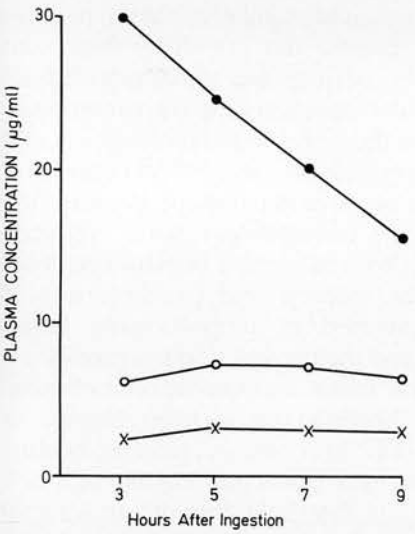

Fig. 2. Plasma concentrations of paracetamol (●) and its glucuronide (○) and sulphate conjugates (×) after a dose of 1.5 g in a patient with a porto-systemic shunt *(Patient 9)*

If the P. T. R. was greater than 1.3, vitamin K_1 (10 mg) was given intramuscularly on 2 successive days and the subsequently measured PTR used.

A complete drug history was taken and whenever possible all drugs were stopped before paracetamol was given. Seven patients had previously been taking drugs regularly: patient 5 prednisolone; patient 7 phenobarbitone; patient 10 frusemide and spironolactone; patient 11 spironolactone and protriptyline; patient 12 bendrofluazide; patient 13 spironolactone and patient 14 bendrofluazide and spironolactone.

All patients were in hospital and stable in their optimal clinical state. None was in cardiac failure whilst only one patient (Patient 8) had a marginally raised plasma urea. Patients 11 and 13 had ascites and patients 1, 4, 10, 12 and 14 oesophageal varices. Patient 9 had previously undergone a lieno-renal shunt; this being patent as judged by the absence of varices. Control studies were carried out in eight healthy male staff volunteers aged 21–34 years with weights ranging from 62–75 kg.

After an overnight fast 1.5 g of paracetamol (Panadol) was given with 40 ml of water after which food and fluids were withheld for 2 h. Venous blood samples were taken at 0, 3, 5, 7 and 9 h after the dose and urine was collected for 24 h. Plasma and urine were stored frozen until assayed for paracetamol and its metabolites by high performance liquid chromatography [11]. The plasma paracetamol half-life was calculated from the linear regression of the logarithms of the plasma concentrations of paracetamol against time using the method of least squares. Student's t-test was used for tests of statistical significance.

Results

Plasma Paracetamol Concentrations and Half-Life

The plasma concentrations of paracetamol in control subjects and patients with liver disease are shown in Figure 1. The patients were divided into two groups, those with mild liver disease (Patients 1–8) in whom serum albumin and/or the P. T. R. were normal, and those with severe liver disease (Patients 9–15) in whom both were abnormal with the exception of the patient with a lieno-renal shunt. The mean plasma paracetamol half-life was similar in normal subjects (2.43 h ± 0.19 SD) and patients with mild liver disease (2.16 h ± 0.54), but was significantly prolonged in those with severe liver disease (4.25 h ± 1.15, $p < 0.001$). The initial mean paracetamol concentration in the patients with severe liver disease (23.2 μg/ml) was almost double that in the controls (12.9 μg/ml) and the patients with mild liver disease (12.2 μg/ml), this difference becoming four-fold at 9 h.

The plasma paracetamol half-life was greater than the mean value ± 2 SD in control subjects in only one of the patients with mild liver disease but in

all those patients with severe disease. In the patients there were significant correlations between the plasma paracetamol half-life and serum albumin ($r = -0.64$: $p = < 0.02$) and P. T. R. ($r = 0.79$: $p = < 0.01$) but not with A. L. T. ($r = 0.17$), alkaline phosphatase ($r = 0.21$) or serum bilirubin ($r = 0.02$).

Paracetamol Metabolites in Plasma

The plasma concentrations of paracetamol glucuronide and sulphate are also shown in Figure 1. In patients with severe liver disease the mean ratios of the plasma concentrations of paracetamol to paracetamol glucuronide and sulphate were more than twice those of the controls at all sampling times (mean values 2.2 and 2.1 respectively). In the mild liver disease patients the corresponding ratios compared with healthy controls were 0.61 and 0.66 respectively.

In the liver disease patients there were statistically highly significant correlations between the individual mean paracetamol to glucuronide and sulphate ratios and paracetamol half-life values ($r = 0.79$ and 0.85 respectively, $p = < 0.001$).

Porto-systemic Shunts

The plasma concentrations of paracetamol and its conjugates in the patient with a lieno-renal shunt are shown in Figure 2. Despite a normal albumin and P. T. R. the plasma paracetamol half-life was considerably prolonged at about 4 h. Very high plasma concentrations of unchanged paracetamol were associated with correspondingly low concentrations of glucuronide and sulphate conjugates consistent with greatly reduced 'first-pass' metabolism. The 3-h plasma paracetamol concentrations and half-lives in patients with and without oesophageal varices (as assessed by a barium swallow examination) did not differ significantly.

Urinary Excretion of Paracetamol and Metabolites

The urinary recovery of paracetamol and its metabolites is shown in Table 2. In normal subjects the mean 24-h urinary recovery of paracetamol and the sulphate, glucuronide, cysteine and mercapturic acid conjugates were approximately 4%, 35%, 55%, 4% and 5% of the dose respectively and there were no important differences between the normal subjects and those with liver disease. However, the total recovery of paracetamol and its metabolites was somewhat less in both groups of patients than in control subjects.

Discussion

The metabolism of paracetamol in the patients with mild liver disease was not depressed as judged by the plasma paracetamol half-life and plasma concentration of metabolites, but was significantly impaired in those with severe liver disease. Although our patients were older than the control subjects, Triggs et al. [12] found only a modest increase in the plasma paracetamol half-life in geriatric subjects with a mean age of 81 years compared with subjects of mean age 24 years. Thus age alone could not account for the differences observed. Nevertheless the overall pattern of the urinary excretion of metabolites in the patients with severe liver disease did not differ from that observed in healthy subjects and patients with mild disease. Of particular significance is the excretion of normal amounts of the cysteine and mercapturic acid conjugates. These two metabolites reflect conversion of the drug to the reactive hepatotoxic intermediate which undergoes conjugation with reduced glutathione [4–7]. With increasing hepatotoxic doses of paracetamol the cysteine and mercapturic acid conugates are excreted in proportionally larger amounts [11, 13] and the present findings provide no evidence to suggest that a therapeutic dose of paracetamol is more likely to cause liver damage in patients with chronic liver disease than in healthy subjects. However, this possibility cannot be ruled out completely as the threshold dose of paracetamol required to produce liver damage depends on the balance of many factors including the rate of paracetamol absorption, the rate of production of the toxic metabolite, hepatic glutathione stores and the maximum rate of glutathione synthesis, all of which could be abnormal in liver disease. Furthermore, our studies were carried out with single doses only. If the intracellular concentrations of glutathione and its rate of synthesis were to be depressed in patients with severe liver disease repeated therapeutic doses of paracetamol could conceivably cause further liver damage. In this context it should be noted that toxic hepatitis has been reported in patients said to have taken high therapeutic doses of the drug [14, 15].

Significant prolongation of the paracetamol half-life has been reported previously in patients with both acute and chronic liver disease [9, 10]. As the mean paracetamol half-life was not prolonged in our patients with a normal serum albumin and/or P. T. R. dosage reduction in such patients would seem unnecessary. Indeed, paracetamol metabolism in these patients may even have been enhanced since the mean plasma concentrations of glucuronide were considerably higher than in the normal subjects. This could be secondary to a reduced renal clearance of

glucuronide and/or microsomal enzyme induction caused by consumption of other drugs and alcohol. On the other hand, when both the P. T. R. and albumin concentrations were abnormal, paracetamol concentrations were high metabolism may be impaired and was thus repeated doses could lead to cumulation and toxicity. Although the hepatic extraction ratio of paracetamol is usually low [10], the higher initial plasma concentrations of unchanged drug in the patients with severe liver disease suggests that this may be due in part to a reduced 'first-pass' hepatic metabolism during absorption. In this context it is of interest that in the patients studied the presence of portal hypertension per se was not necessarily associated with an increased plasma paracetamol concentration or half-life. However in the patient with the lieno-renal shunt there was evidence of markedly reduced 'first-pass' metabolism. Thus although the patient had a normal serum albumin and P. T. R. plasma paracetamol concentrations were very high, with slow metabolism, a prolonged half-life and low plasma concentrations of the metabolites. Particular care is therefore needed when oral drugs with high hepatic extraction ratios are prescribed for such patients.

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